



New therapies for obesity

Papamargaritis, D., le Roux, C. W., Holst, J. J., & Davies, M. J. (2022). New therapies for obesity. *Cardiovascular Research*, [cvac176]. <https://doi.org/10.1093/cvr/cvac176>

[Link to publication record in Ulster University Research Portal](#)

Published in:
Cardiovascular Research

Publication Status:
Published online: 30/11/2022

DOI:
[10.1093/cvr/cvac176](https://doi.org/10.1093/cvr/cvac176)

Document Version
Peer reviewed version

General rights

Copyright for the publications made accessible via Ulster University's Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Ulster University's institutional repository that provides access to Ulster's research outputs. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact pure-support@ulster.ac.uk.

1 **Manuscript title:** New therapies for obesity

2 **Authors:** Dimitris Papamargaritis¹, Carel W le Roux^{2,3}, Jens J Holst⁴, Melanie J Davies¹.

3

4 **Correspondence to:**

5 Dr Dimitris Papamargaritis, Diabetes Research Centre, Leicester General Hospital, University of
6 Leicester College of Medicine Biological Sciences and Psychology, Leicester, UK

7 **Telephone:** +44 (0)116 258 8973 **email:** dp421@leicester.ac.uk

8 **Affiliations:**

9 ¹Diabetes Research Centre, Leicester General Hospital, University of Leicester College of
10 Medicine Biological Sciences and Psychology, Leicester, UK

11 ²Diabetes Complications Research Centre, Conway Institute, University College Dublin, Dublin,
12 Ireland

13 ³Diabetes Research Centre, Ulster University, Coleraine, UK

14 ⁴Department of Biomedical Sciences and the NNF Center for Basic Metabolic
15 Research, University of Copenhagen Panum Institute, Copenhagen, Denmark

16 **Key words:** obesity, pharmacotherapy, bariatric surgery, semaglutide, tirzepatide, liraglutide

17 **Category of manuscript:** Invited review article

18 **Word count (abstract, manuscript, references and figure legends):** 14980 words

1 Abstract

2 Obesity is a chronic disease associated with serious complications and increased mortality.

3 Weight loss through lifestyle changes results in modest weight loss long-term possibly due to
4 compensatory biological adaptations (increased appetite and reduced energy expenditure)
5 promoting weight gain. Bariatric surgery was until recently the only intervention that
6 consistently resulted in $\geq 15\%$ weight loss and maintenance. Our better understanding of the
7 endocrine regulation of appetite has led to the development of new medications over the last
8 decade for treatment of obesity with main target the reduction of appetite.

9 The efficacy of semaglutide 2.4mg/week - the latest glucagon like peptide-1 (GLP-1) receptor
10 analogue - on weight loss for people with obesity suggests that we are entering a new era in
11 obesity pharmacotherapy where $\geq 15\%$ weight loss is feasible. Moreover, the weight loss
12 achieved with the dual agonist tirzepatide (GLP-1/ glucose-dependent insulinotropic
13 polypeptide) for people with type 2 diabetes and most recently also obesity, indicate that
14 combining the GLP-1 with other gut hormones may lead to additional weight loss compared to
15 GLP-1 receptor analogues alone and in the future, multi-agonist molecules may offer the
16 potential to bridge further the efficacy gap between bariatric surgery and the currently available
17 pharmacotherapies.

18 This article provides a review of the currently available interventions for weight loss and weight
19 maintenance with a focus on pharmacological therapies for obesity approved over the last
20 decade, as well as the emerging development of new obesity pharmacotherapies.

21

1

2 **1. Introduction**

3 Obesity is a complex, chronic, progressive and relapsing disease characterized by abnormal or
4 excessive body fat that impairs health.¹ It is one of the greatest global public health challenges,
5 considering that 13% of the global population lives with obesity and that its prevalence has been
6 tripled since 1975.² Obesity drives the pathogenesis of multiple metabolic and mechanical
7 complications including type 2 diabetes (T2D), hypertension, dyslipidaemia, sleep apnoea,
8 cardiovascular disease, non-alcoholic fatty liver disease, infertility and osteoarthritis³ which
9 result in a decreased life expectancy of 5–20 years and increased healthcare costs.⁴⁻⁷

10 Lifestyle interventions are the cornerstones for the management of obesity, but even the most
11 intensive programmes still commonly only achieve 5-10% weight loss (WL) and long-term
12 weight maintenance remains a challenge.⁸ Although 5-10% WL reduces cardiometabolic risk
13 factors it may not be enough to make a difference to the lives of people with BMI ≥ 35 kg/m²
14 (class II obesity and above) and/or to reverse some obesity related complications such as sleep
15 apnoea and T2D.^{9, 10} Until recently, pharmacotherapy to achieve and maintain $\geq 10\%$ WL along
16 with suitable tolerability and safety remained an unmet challenge. Bariatric surgery was the only
17 intervention that consistently resulted in $\geq 15\%$ WL and weight maintenance long-term.¹¹ This
18 amount of WL led to improved quality of life (QoL), significant health benefits and reduced
19 mortality.¹¹⁻¹³ Despite the considerable benefits of bariatric surgery, it is not feasible or scalable
20 as a population-wide intervention. Recent clinical trials with advanced therapeutic candidates
21 including new glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dual agonists
22 demonstrate that the gap of sustained WL between bariatric surgery and pharmacotherapy is
23 gradually closing.^{14, 15}

1 Here, we review the available interventions for WL and weight maintenance with a focus on
2 pharmacological therapies for obesity approved over the last decade as well as the emerging
3 development of new obesity pharmacotherapies. We also discuss the future directions of obesity
4 pharmacotherapy and the research priorities to support implementation of these treatments in
5 clinical practice.

6

7 **2. Obesity treatments**

8 **2.1 Lifestyle interventions**

9 Lifestyle interventions usually include support for health-improving behavioural changes
10 including diet, increasing physical activity and reducing sedentary time. Moderate intensity
11 lifestyle interventions such as 500-600 kcal deficit diet together with advice to increase physical
12 activity to 150 min/week usually lead to a WL of 2-5% at 12 months and weight maintenance
13 remain a challenge.

14 Intensive lifestyle interventions, which often include partial or total meal replacements, intensive
15 behavioural therapy (IBT) and/or structured exercise, can lead up to $\approx 10\%$ WL at the end of the
16 first year.^{16,17}

17 In the DROPLET study, a community delivered, low energy (810 kcal/day) total diet
18 replacement programme with formula products as the sole food during the first eight weeks
19 followed by food reintroduction resulted in mean WL of 10.7kg at 12 months compared to 3.1kg
20 at the usual care group in people with obesity.¹⁸ However, at the 3 year follow-up, mean WL was
21 6.2kg at the intervention arm compared to 2.7kg at the usual care¹⁹ with 24% of participants

1 achieving $\geq 10\%$ WL in the total diet replacement programme compared to 13% in usual care,
2 suggesting that for this smaller number of patients this treatment was effective.¹⁹

3 Structured exercise programmes can usually add 1.5-3.5kg WL to a dietary intervention and they
4 have multiple other health benefits such as improvement in body composition, physical function
5 and cardiorespiratory fitness.²⁰ There is limited evidence on the effect of structured exercise on
6 weight maintenance after weight-loss through diet,²⁰ but a recent clinical trial showed that the
7 addition of a 52-week structured but flexible aerobic exercise programme after a low calorie diet
8 programme (mean WL 12%) can lead to 4.1kg less weight gain compared to people who
9 continue with their usual physical activity.²¹ However, long-term maintenance of the
10 recommended amount of moderate to vigorous physical activity can be challenging.²²

11
12 The largest trial assessing the effectiveness of intensive lifestyle interventions was the Look
13 AHEAD study, where 5145 people with obesity and T2D were randomized to receive intensive
14 lifestyle support (intervention group) vs a structured education programme (usual care group).²³
15 The intensive lifestyle group lost 8.6% of their initial body weight at 1 year and 4.7% at 8 years
16 while the usual care arm lost 0.7% at 1 year and 2.1% at 8 years.⁸ In the intensive lifestyle group,
17 37.7% of study participants achieved $\geq 10\%$ WL at 1 year postoperatively and 39.3% of them
18 (324/2144, 15.1% of the total population at the intensive lifestyle group) were able to maintain
19 $\geq 10\%$ WL for 8 years.⁸

20 Overall, the Look AHEAD intervention did not demonstrate a reduction in cardiovascular events
21 or a reduction at the risk for new onset heart failure or atrial fibrillation.²⁴⁻²⁶ However, in a
22 posthoc analysis, those participants in the intervention arm who lost $\geq 10\%$ of their baseline body

1 weight during the first year (early good responders) had 20% lower risk for cardiovascular events
2 over a 10 years follow-up period.²⁷ Similarly, a 10% decrease in BMI over the first year in
3 participants at the Look AHEAD study was associated with a 31% lower risk of incident heart
4 failure, when a 10% decrease in BMI over a 4-year follow-up period was associated with a 20%
5 lower risk of incident heart failure.²⁵ These results suggest that $\geq 10\%$ WL is associated with
6 cardiovascular benefits for people with obesity and T2D. Moreover, the REVERSE-AF study
7 also showed that $\geq 10\%$ weight reduction results in 88% reversal from persistent to paroxysmal or
8 no atrial fibrillation.²⁸

9 In general, weight regain is common after lifestyle interventions and approximately 80% of
10 weight lost is expected to be regained over the next 5 years.²⁹ Only 10-25% of individuals who
11 will undergo different intensity lifestyle interventions will be able to lose and maintain $\geq 10\%$
12 WL long-term. The rest of individuals could be considered non-responders to the lifestyle
13 intervention and will need further interventions to achieve and maintain significant WL.

15 **2.1.1 Why is it so challenging to maintain weight loss with lifestyle changes?**

16 The weight regain after significant WL with lifestyle changes is not simply attributable to the
17 loss of motivation or compliance from the patients. Instead, it is driven by potent biological
18 mechanisms that stimulate food intake and reduce energy expenditure on the background of an
19 “obesogenic” environment, where ultra-processed, high-calorie foods are easily accessible,
20 physical activity is reduced and sedentary time increased.^{30, 31} The major drivers of weight regain
21 after treatments that caused significant WL, include the persistence of a lower resting metabolic
22 rate (metabolic adaptation), the lower energy consumption during weight-bearing activities and

1 the persistence of increased appetite, probably mediated through long-lasting increased
2 orexigenic and decreased anorexic signals.^{30,31} Overall, the increased appetite and the reduced
3 energy expenditure during the weight reduced state results in a feeling of constant and
4 exhausting effort to maintain the achieved WL and to prevent the seemingly unavoidable weight
5 regain over time.^{30,32}

6 Resting metabolic rate (RMR) is mainly determined by body composition and accounts for 60-
7 70% of 24 hours total energy expenditure in humans.^{31,33} However, RMR in response to WL is
8 often reduced to a greater extent than would be expected based on the measured changes in body
9 composition. This physiological mechanism is called “metabolic adaptation” and is one of the
10 reasons why the body resists further WL and individuals regain weight so easily.³³ For example,
11 the participants of the “Biggest Loser” television program lost, on average, 40% of their body
12 weight, and their mean RMR decreased by 610 kcal/day – this was on average 275 kcal/day
13 lower compared to what was expected based on their body composition.³⁴ This metabolic
14 adaptation persisted six years later despite regaining two-thirds of the lost weight.^{33,34}

15 In addition, most people who manage to lose $\geq 10\%$ of their body weight through low calorie diet
16 experience an increase in their appetite compared to baseline (Figure 1).³⁵ Potential mediators of
17 the increased appetite are the elevated levels of the hunger hormone ghrelin as well as the
18 reduction in leptin and perhaps also satiety gut hormones such as peptide YY (PYY), amylin and
19 cholecystokinin.³⁵ These changes remain even after 52 weeks from the completion of the low
20 calorie diet and despite that participants experience weight regain, for instance 5.5 kg at the end
21 of the cited study.³⁵ Studies assessing the appetite-related responses during and after single bouts
22 of continuous aerobic exercise indicate that subjective feelings of appetite are transiently
23 suppressed during exercise in people with obesity; but energy intake is minimally affected.^{36,37}

1 Regarding the chronic effects of aerobic exercise on appetite parameters, the results are
2 inconsistent - however a small increase in hunger at fasting state with a subsequent increase in
3 satiety post-meal and without significant increase on energy intake has been found in a recent
4 systematic review and meta-analysis.^{36, 38}

5 Increased appetite likely plays a quantitatively greater role on weight regain than the decreased
6 energy expenditure because the feedback circuits controlling long-term energy intake have
7 greater overall strength compared with the feedback circuits controlling energy expenditure.^{30, 32}

8 So, if we consider obesity as a disease of dysregulated appetite where the increased hunger
9 and/or the reduced satiety are the main symptoms,³⁹ then lifestyle interventions which usually
10 result in increase of appetite may not effectively treat the symptoms of the underlying disease
11 and this will lead in the majority of the cases to weight regain long-term despite the successful
12 initial weight loss. However, weight loss maintenance can occur in a smaller number of people
13 who despite WL with lifestyle interventions do not experience increased appetite, suggesting that
14 lifestyle interventions can also be considered as effective obesity treatments in a small number of
15 patients and that there is individual variability in response to different lifestyle interventions
16 regarding appetite signals and weight regain.^{31, 40}

17 Anti-obesity medications can also effectively treat obesity by counteracting the increased drive
18 to eat and the impaired satiation associated with WL by lifestyle changes and could help with
19 further WL and weight maintenance.⁴¹⁻⁴³ However, as with most management techniques for
20 chronic diseases, obesity relapses if the treatment is stopped.⁴⁴

21

22

1 2.2 The example of bariatric surgery

2 Bariatric surgery is a collective term for surgical treatment of obesity. It is so far the most
3 successful existing approach for safe and effective obesity treatment and results in sustained WL
4 while at the same time reduces appetite.^{11, 45} In the Swedish Obese Subjects (SOS) study,
5 bariatric surgery was able to induce and maintain $\geq 15\%$ mean WL over 20 years follow-up
6 (compared to 1% WL at the usual care group).¹¹ This amount of sustained WL was associated
7 with improvement in QoL and obesity related complications, reduction by 53% in fatal and 33%
8 in total cardiovascular events, and reduction by 29% in mortality compared to the usual care
9 group,^{11, 12, 46, 47} providing a WL threshold associated with multiple clinically important benefits.
10 Moreover, bariatric surgery in SOS study reduced the risk for new onset heart failure by 35%
11 and for new diagnosis of atrial fibrillation by 29% compared to the usual care group.^{48, 49} The
12 benefits of bariatric surgery on reducing cardiovascular events, cardiovascular death, all-cause
13 mortality and new onset heart failure compared to the non-surgical management are consistent
14 across multiple observational, matched-cohort studies, especially in people with obesity and
15 T2D.^{50, 51}

16 The most commonly performed bariatric procedures in the SOS study were gastric band and
17 vertical banded gastroplasty with fewer patients undergoing Roux-en-Y gastric bypass
18 (RYGB).¹¹ Today, the two most commonly performed bariatric procedures ($\approx 85\%$ of bariatric
19 procedures worldwide) are sleeve gastrectomy (SG) and RYGB.⁵² RYGB results in 30% WL
20 over the first postoperative year and a sustained 25-27% WL long-term.^{11, 53} SG leads to 25%
21 WL at the first postoperative years and around 20% WL long-term.⁵³ Weight loss and WL
22 maintenance after bariatric surgery are achieved as a consequence of voluntary reduced food
23 intake due to reduced appetite (Figure 1) rather than through restriction, malabsorption or

1 increased energy expenditure.⁵⁴ One of the potential mediators for the reduced appetite and food
2 intake after bariatric surgery is the changes in the peripheral signals of body weight regulation
3 (how the gut communicates with the brain) through alteration of gut anatomy. More specifically,
4 both RYGB and SG substantially increase the secretion of multiple satiety gut hormones after
5 food intake, including GLP-1 and PYY and when the action of these hormones was blocked after
6 RYGB, the food intake increased by 20%,⁵⁵ supporting a role of these gut hormones in early
7 postprandial satiety.

8 However, not every person with severe and complex obesity wants or is fit enough to undergo
9 surgery, and there is no surgical capacity to operate on every person that qualifies for bariatric
10 surgery. So, pharmacotherapies mimicking some of the postoperative physiological changes after
11 bariatric surgery would be a logical approach to try to achieve similar weight loss.

13 **2.3 Approved pharmacotherapies for obesity over the last decade**

14 Numerous obesity medications targeting appetite and reward centres have been tried in the past
15 to support WL but the majority has been withdrawn due to safety concerns.⁵⁶⁻⁵⁸ For example,
16 sibutramine was withdrawn due to increased risk of cardiovascular events (myocardial infarction
17 and non-fatal stroke) in people with obesity and pre-existing cardiovascular conditions when
18 rimonabant was withdrawn due to increased risk of psychiatric adverse events including
19 depressed mood disorders, anxiety and suicide.^{57,58} More recently, lorcaserin was withdrawn
20 from the market because of a signal of increased cancer risk.⁵⁹ Nevertheless, the better
21 understanding over the last years of the peripheral and central signals and mechanisms involved
22 in WL and WL maintenance have contributed to the development of more effective and safe

1 weight-loss medications. Orlistat, which was approved in 1999 for obesity treatment have
2 demonstrated its safety and efficacy in multiple trials, but it has, at best, modest effect (WL 3-
3 5%) as result of reduced absorption of ingested fat and behavioural changes (to avoid
4 steatorrhea).⁶⁰

5 Over the past decade, several agents that act by reducing hunger or promote satiation have been
6 approved by regulatory authorities worldwide for chronic weight management, including
7 phentermine plus topiramate (approved only in the US), bupropion plus naltrexone, and the
8 GLP-1 RAs liraglutide 3mg and semaglutide 2.4mg.

10 **2.3.1 Phentermine – Topiramate**

11 Phentermine-Topiramate (PHEN-TPM) is an oral medication approved for obesity treatment in
12 the US, but not in Europe due to concerns about the medication's long-term cardiovascular
13 safety. The fixed-dose combination approved in the US contains phentermine (PHEN) doses
14 from 3.75 to 15 mg and topiramate (TPM) doses from 23 to 92 mg for daily administration.

15 PHEN is a sympathomimetic amine which acts as an appetite suppressant via the central nervous
16 system.⁶¹ It is indicated for short-term use in weight management in US, however long-term data
17 is not available. TPM is an anticonvulsant indicated for use in the treatment of migraine and
18 epilepsy.⁶¹ One of the known effects of TPM is also a decrease in appetite.

19 In people without diabetes, 56 weeks of PHEN-TPM 15/92 extended release (ER) in
20 combination with 500 kcal/day deficit diet resulted in 10.9% WL compared to 1.6% with placebo
21 and 32.3% of participants achieved more than $\geq 15\%$ WL.⁶² Similar results were reported at the

1 2-year follow-up of PHEN-TPM 15/92 ER⁶³ (Table 1). In people with T2D, 56 weeks of PHEN-
2 TPM ER 15/92 reduces body weight by 9.6% compared to 2.6% with placebo and improved
3 HbA1c by 1.6% (17.5 mmol/mol) compared to 1.2% (13.1 mmol/mol) with placebo⁶⁴ (Table 2).
4 The most commonly reported adverse events are upper respiratory tract infection, constipation,
5 insomnia, paraesthesia, sinusitis, taste change and dry mouth.^{62, 63, 65} PHEN-TPM has also a
6 warning of birth defects (cleft lip and palate) in the offspring of pregnant women taking the
7 medication, due to the known teratogenic effect of TPM.

8 The improvement in weight with PHEN/TPM was associated with improvements in QoL⁶⁶ and
9 cardiometabolic risk factors.^{62, 63, 65} A retrospective analysis of PHEN used concurrently with
10 TPM, either separately or in fixed-dose combination showed a trend for a lower rate of major
11 adverse cardiovascular events (MACE) and other cardiovascular outcomes among those
12 receiving PHEN/TPM (including the fixed-dose combination) than among the unexposed cohort
13 (HR: 0.24; 95% CI, 0.03 to 1.70 for fixed dose PHEN-TPM).⁶⁷ However, the cardiovascular
14 safety of this treatment requires evaluation in an adequately powered outcome trial.

15

16 **2.3.2 Naltrexone – Bupropion**

17 Naltrexone is an opioid receptor antagonist that is approved for the treatment of alcohol and
18 opioid dependence.⁶⁸ Bupropion is a dopamine and norepinephrine reuptake inhibitor that was
19 first approved for the treatment of depression and later for smoking cessation.⁶⁸ The exact
20 mechanism whereby the naltrexone/bupropion (NB) combination leads to WL is not fully
21 understood, but it is likely that it promotes satiety, reduces food intake and may enhance energy
22 expenditure through actions at the hypothalamus and mesolimbic dopamine circuit. Participants

1 in clinical trials who responded to NB as an obesity treatment reported feeling less hungry and
2 more full compared to those receiving placebo and they found it easier to control their food
3 cravings.⁶⁹

4 In people without diabetes, NB 32/360 together with a 500 kcal deficit diet resulted in 6.3% WL
5 at 52 weeks compared to 0.9% in the placebo group.⁶⁹ In COR-I and COR-II studies, 25% to
6 28.3% of those on NB 32/360 achieved $\geq 10\%$ WL.^{69,70} Additionally, NB 32/360 in combination
7 with an IBT program and diet resulted in 9.3% WL vs 5.1% with placebo.⁷¹ In people with
8 obesity and T2D, NB 32/360 resulted in 5% mean WL at 56 weeks compared to 1.8% with
9 placebo.⁷² 26.3% of participants receiving NB 32/360 achieved $\geq 10\%$ WL and HbA1c was
10 reduced by 0.6% compared to 0.1% in those receiving placebo.⁷²

11 The most common adverse events with NB 32/360 are nausea, headache, constipation, dry
12 mouth, anxiety, dizziness, hypertension and vomiting.^{69,72} The NB is contraindicated in people
13 with epilepsy as bupropion is associated with dose-related risk of seizures.

14 Physical function and self-esteem improved with NB 32/360 compared to placebo.^{73,74} The WL
15 achieved with NB 32/360 was also associated with improvements in some cardiometabolic risk
16 factors such as HDL and hepatic insulin resistance markers, however the systolic blood pressure
17 (SBP) and diastolic blood pressure (DBP) improved more in the placebo group compared to the
18 NB 32/360.⁷⁰

19 A clinical trial on cardiovascular outcomes for NB was terminated early due to early release of
20 the interim analysis performed after 50% of planned events (HR, 0.88; adjusted 99.7% CI, 0.57-
21 1.34 compared to placebo).⁷⁵ So, the cardiovascular safety of NB remains uncertain and will
22 require further reevaluation in adequately powered outcome trials.

1

2 **2.3.3 Currently approved pharmacotherapies for obesity based on gut hormones**

3 **2.3.3.1 GLP-1 Receptor Agonists (GLP-1 RA)**

4 GLP-1 is an incretin hormone secreted predominantly from L cells located in the small intestine
5 in response to food intake.⁷⁶ In addition to the glucose-lowering actions such as stimulation of
6 glucose-induced insulin secretion, delay in gastric emptying and inhibition of glucagon secretion,
7 exogenous GLP-1 infusion in humans resulted recurrently in reduced calorie intake, reduced
8 appetite and effects on the reward system without direct changes in energy expenditure.⁷⁷⁻⁷⁹

9 GLP-1 RAs have been developed initially for the treatment of T2D, however due to their
10 efficacy in inducing WL and reducing appetite, they have been repurposed in higher doses as
11 treatments for obesity. Exogenous GLP-1 and GLP-1 RAs may predominantly access the brain
12 via the leaks in the blood-brain barrier, where the underlying neuronal tissue shows a dense
13 expression of GLP-1 receptors. In animal experiments, the effect of GLP-1 RAs on food intake is
14 entirely dependent on central nervous system mechanisms,⁸⁰ and in humans this is supported by
15 imaging experiments.^{81, 82}

16

17 **2.3.3.2 Liraglutide 3mg**

18 In 2014, liraglutide 3mg once daily became the first GLP-1 RA to be approved for the treatment
19 of adults with obesity and in 2021 it was also approved for adolescents ≥ 12 years old.⁸³

20 Liraglutide 3mg is a long-acting GLP-1 RA and mechanistic studies have demonstrated that it
21 increases postprandial satiety and fullness, reduces hunger and prospective food consumption

1 and decreases ad libitum food intake at lunch by $\approx 16\%$ (136 kcal).⁴³ Moreover, the mean 24-h
2 energy expenditure was reduced by $\approx 5\%$ (139 kcal), which was mainly explained by the decrease
3 in food intake and body weight (Figure 1).⁴³

4 Liraglutide 3mg in combination with a 500 kcal/day deficit diet resulted in 6.1-8% WL in adults
5 without diabetes (Table 1).^{84, 85} For people with T2D, liraglutide 3mg resulted in 5.8% - 6% WL
6 compared to 1.5% - 2% WL with placebo (Table 2).^{86, 87} HbA1C reduced by 1.6% with
7 liraglutide 3mg and 0.4% with placebo.^{86, 87}

8 Liraglutide 3mg is also effective for weight maintenance after initial WL through diet
9 intervention. In SCALE-Maintenance study, after a 5% WL obtained via a diet over 4-12 weeks,
10 liraglutide 3mg resulted in further 6.1% WL at 56 weeks compared to placebo (6.2% vs 0.2%).⁴¹

11 The most common side effects include mild to moderate gastrointestinal problems such as
12 nausea, diarrhoea, constipation and (more rarely) vomiting which occurred primarily within the
13 first 4 to 8 weeks after initiation of liraglutide treatment.^{84, 87} Pancreatitis, a rare side effect of
14 GLP-1 RA was reported in 0.7% of participants at liraglutide 3mg arm [0.3 events per 100
15 person-years of observation (PYO)] at the 3-year follow-up of SCALE-Prediabetes trial
16 compared to 0.3% of participants at placebo arm (0.1 events per 100 PYO) and the vast majority
17 of the cases were graded as mild.⁸⁸

18 The QoL and especially the physical function improved more with use of liraglutide 3mg
19 compared to placebo, with people achieving $\geq 15\%$ WL having the most benefit.⁸⁹ In addition,
20 WL with liraglutide 3mg improves also multiple other obesity-related complications, including
21 reduction in T2D incidence by 79% in people with prediabetes after 3 years of treatment
22 compared to placebo⁸⁸ and reduction in apnoea-hypopnea index in people with sleep apnoea

1 [however, without change in requirement of continuous positive airway pressure (CPAP)
2 support].⁹⁰

3 Liraglutide 1.8mg (dose approved for T2D treatment) was shown to reduce cardiovascular events
4 in patients with T2D and established cardiovascular disease (LEADER trial) followed for up to 5
5 years⁹¹. On the other hand, in a 24-week clinical trial in people with chronic heart failure (left
6 ventricular ejection fraction $\leq 45\%$, n=241) with and without diabetes, liraglutide 1.8mg once
7 daily did not improve the left ventricular systolic function compared to placebo and raised some
8 concerns regarding cardiac safety of the medication at this population.⁹² However, a subanalysis
9 of LEADER trial [including 1667 people with T2D and heart failure at baseline, New York Heart
10 Association (NYHA) functional class I to III] found that the beneficial effects of liraglutide
11 1.8mg vs placebo on major cardiovascular events and mortality were consistent in people with
12 and without heart failure and there was no difference between the two groups in hospitalisation
13 for heart failure, suggesting that liraglutide 1.8mg use is safe for people with T2D and heart
14 failure (NYHA class I to III).⁹³

15 Liraglutide 3mg (dose approved for obesity treatment) has been shown to improve multiple
16 cardiometabolic risk factors, but studies to evaluate cardiovascular outcomes in people with
17 obesity have not been done. An analysis of data from SCALE programme demonstrated that
18 liraglutide 3mg use was not associated with excess cardiovascular risk compared to comparators
19 (HR 0.42, 95% CI 0.17 – 1.08), however the confidence interval was wide.⁹⁴

20

21

1 2.3.3.3 Semaglutide 2.4mg

2 Semaglutide 2.4mg once weekly is a new long-acting GLP-1 RA which was approved in 2021
3 for treatment of obesity in the US and Europe. Semaglutide 2.4mg reduces energy intake in
4 people with obesity during an ad libitum lunch by 35% (-224 kcal vs placebo) through appetite
5 reduction.⁴² People receiving semaglutide reported reduced hunger, increase in fullness and
6 satiety, better control of eating and fewer and weakened food cravings.⁴² Moreover, the rate of
7 gastric emptying was reduced as well as the prospective food consumption for participants
8 receiving semaglutide 2.4mg.⁴²

9 In clinical trials, 56 weeks of semaglutide 2.4mg in combination with a 500 kcal/day deficit diet
10 resulted in 14.9% WL vs 2.4% with placebo in people without diabetes.¹⁵ 50.5% of those
11 receiving semaglutide 2.4mg achieved $\geq 15\%$ WL and 32% achieved $\geq 20\%$ WL compared to
12 4.9% and 1.7% respectively at the placebo group (Table 1).¹⁵ In direct comparison with
13 liraglutide 3mg, semaglutide 2.4mg results in more than double WL (Table 1, STEP-8).⁹⁵
14 Additionally, 68 weeks of semaglutide 2.4mg in combination with IBT and a low calorie diet
15 during the first 8 weeks resulted in 16% WL vs 5.7% in the placebo group.⁹⁶

16 In people with T2D, WL with semaglutide 2.4mg once weekly was 9.6% vs 7% with
17 semaglutide 1mg once weekly (dose approved for T2D treatment) and 3.4% with placebo (Table
18 2).⁹⁷ HbA1c was reduced by 1.6% at 68 weeks with semaglutide 2.4mg compared to 1.5% with
19 semaglutide 1mg and 0.4% with placebo (Table 2).⁹⁷

20 Why semaglutide and liraglutide are less effective in people with T2D compared to populations
21 without diabetes is not fully understood, but the different population demographics in the T2D
22 clinical trials (higher percentage of men), the use of background glucose-lowering medications

1 that can contribute to weight gain (such as sulphonylureas) and the reduction of glycosuria due to
2 improvement of glycaemic control with GLP-1 RAs may contribute to these results.⁹⁸

3 Weight loss with semaglutide was associated with improvements in QoL and participants in the
4 semaglutide group were more likely to have clinically meaningful within-person improvements
5 in physical function than with placebo.¹⁵ Mild to moderate gastrointestinal problems such as
6 nausea, vomiting and diarrhoea were the most common side effects of semaglutide.^{15, 99} Adverse
7 events leading to discontinuation of semaglutide 2.4mg ranged between 3% and 7% in STEP
8 programme.^{15, 95-97, 100, 101} Acute pancreatitis was reported in 0.2% of participants at the STEP-1
9 trial (0.2 events per 100 PYO).¹⁵

10 Despite the improvement in multiple cardiovascular risk factors with semaglutide 2.4mg, the
11 cardiovascular safety profile has not yet been confirmed in people with obesity. A large clinical
12 trial (SELECT, NCT03574597) is currently taking place to assess the effect of semaglutide on
13 major cardiovascular outcomes in people with obesity and established cardiovascular disease.
14 However, in SUSTAIN 6 study, semaglutide 1mg in people with T2D and established
15 cardiovascular disease resulted in reduction of major adverse cardiovascular events by 26%
16 compared to placebo (mainly due to reduction in stroke incidence), providing some
17 reassurance.¹⁰² In SUSTAIN-6, there was no effect of semaglutide 1mg compared to placebo on
18 hospitalization for heart failure,¹⁰² but the impact of semaglutide 2.4mg in people with heart
19 failure with preserved ejection fraction and obesity will be assessed at the ongoing STEP-HFpEF
20 (NCT04788511) and STEP-HFpEF DM (NCT04916470) trials.

21

1 Finally, oral semaglutide - an approved treatment for T2D at the doses of 7 and 14mg once daily
2 - is currently undergoing phase 3 trials as treatment for obesity at the dose of 50mg once daily. In
3 a phase 2, dose-finding trial, 40mg of oral semaglutide in people with T2D resulted in 6.9% WL
4 compared to 6.4% with injectable semaglutide 1mg and 1.2% with placebo.¹⁰³

5

6 **2.3.4 Summary of approved pharmacotherapies for obesity management**

7 Until 2021, the approved pharmacotherapies for chronic weight management
8 (phentermine/topiramate, bupropion/naltrexone, liraglutide 3mg, orlistat) could result in 5-10%
9 mean WL and WL maintenance when combined with moderate intensity lifestyle interventions.
10 In 2021, Semaglutide 2.4mg once weekly became the first approved obesity pharmacotherapy
11 which leads to \approx 15% WL in people without diabetes when combined with moderate intensity
12 lifestyle interventions, which almost doubles the effectiveness on WL over previous obesity
13 pharmacotherapies with a good tolerability and safety profile in clinical trials.

14

15 **3. Emerging treatments for obesity**

16 **3.1 Gut hormones - Dual agonists and triple agonists**

17 Although GLP-1 RAs and especially semaglutide are effective treatments for obesity and T2D,
18 there is still significant efficacy gap regarding WL between the currently available
19 pharmacotherapies and bariatric surgery (Figures 2A and 2B). Based on the example of bariatric
20 surgery where multiple gut hormones are increased postoperatively, the combination of GLP-1
21 with other gut hormones such as glucose-dependent insulinotropic peptide (GIP), glucagon,

1 amylin and PYY may complement and enhance further the GLP-1 effect leading to additional
2 WL, increased energy expenditure and improved metabolic outcomes.¹⁰⁴

3 Tirzepatide is the first dual co-agonist (acting on GLP-1/GIP receptors) which has been approved
4 for treatment of T2D at the US (May 2022) based on the findings of the clinical trials from the
5 SURPASS programme. Moreover, tirzepatide is currently undergoing an extensive programme
6 of phase 3 clinical trials as treatment for obesity (SURMOUNT). The recently published
7 SURMOUNT-1 trial randomised 2539 participants with obesity (without diabetes) to three
8 different doses of tirzepatide (5, 10 and 15mg, n=1896) or placebo (n=643) with follow-up 72
9 weeks and showed that tirzepatide 5-15mg results in 15-20.9% WL when combined with
10 moderate intensity lifestyle interventions compared to 3.1% WL with placebo.¹⁰⁵

11 Other dual co-agonists acting on GLP-1/amylin receptors and GLP-1/glucagon receptors are also
12 being assessed in early phase clinical trials as potential treatments for obesity and metabolic
13 complications.^{106, 107} Moreover, triple agonists, for example GLP-1/GIP/glucagon agonists are
14 being explored as potential treatments, although data from clinical trials are limited and in early
15 stage.

17 **3.2 GLP-1/GIP combinations for people with obesity and T2D**

18 GIP is a 42-amino acid peptide secreted by endocrine K cells in the duodenum and jejunum in
19 response to nutrient ingestion and is an incretin hormone. In people without diabetes, GIP
20 stimulates insulin secretion but does not change glucagon release during hyperglycaemia,
21 whereas it increases glucagon release without affecting insulin secretion during

1 hypoglycaemia.^{108, 109} In the context of T2D, the ability of GIP to stimulate insulin secretion and
2 to ameliorate glycaemia is impaired.¹¹⁰

3 Regarding the effect of GIP on appetite, it has only been assessed in a few acute studies in
4 humans.^{82, 111, 112} Unlike GLP-1, exogenous GIP infusion does not seem to reduce appetite and
5 the combination of GLP-1 with GIP in people with and without T2D does not lead to any more
6 significant appetite reduction compared to GLP-1 alone.⁸²

7 On this background, it came as a surprise that the GLP-1/GIP co-agonist, tirzepatide, had
8 glucose-lowering and weight-loss activities that exceeded those of GLP-1 RA comparators in
9 clinical trials.^{113, 114} Tirzepatide is a once weekly unimolecular agonist of both GLP-1 and GIP
10 receptors which has a deliberate bias towards GIP over GLP-1 activity (it possesses fivefold
11 increased relative potency at human GIP receptor as compared with GLP-1 receptor).¹¹⁵ This has
12 been provided as a potential explanation for the more prominent effects on weight and glucose
13 compared to the more balanced dual agonists targeting GLP-1 and GIP receptors equally
14 (although this is difficult to understand given that GIP alone has no effect on food intake in
15 man). Further research is required to understand the mechanisms mediating the effects of
16 tirzepatide on weight and glycaemia. Compared to GLP-1, however, tirzepatide acts as a biased
17 agonist with little beta-arrestin recruitment and receptor internalization, which may explain the
18 superior activity on target cells.¹¹⁶

19
20 The phase 3 trials with tirzepatide doses 5 to 15mg in people with T2D who are overweight or
21 have obesity (SURPASS programme) have shown marked improvements both on WL and
22 glycaemia, despite that tirzepatide in SURPASS programme was not combined with lifestyle
23 changes (as primary outcome was improvement in glycaemia rather than WL), such as in the

1 SCALE and STEP programmes. In SURPASS-3 study, 52 weeks of tirzepatide 15 mg led to
2 mean WL of 11.3kg (treatment-policy estimand) compared to 1.9kg weight gain with insulin
3 degludec and 35% of those on tirzepatide 15mg were able to achieve $\geq 15\%$ WL compared to 0%
4 at the insulin degludec group (Table 2).¹¹⁷ Moreover, HbA1c reduced with tirzepatide 15mg by
5 2.14% (treatment-policy estimand) in SURPASS-3.¹¹⁷ Similar findings regarding WL and
6 glycaemic improvement after 52 weeks of tirzepatide use were also reported at the SURPASS-4
7 trial (Table 2).¹¹⁸

8 In direct comparison with semaglutide 1mg (dose for treatment of T2D), tirzepatide 15mg led to
9 5.5kg more WL at 40 weeks and 36% of people achieved $\geq 15\%$ WL compared to 8% with
10 semaglutide 1mg (SURPASS-2).¹¹³ Tirzepatide 15mg resulted also in an HbA1c reduction of
11 0.45% more compared to semaglutide 1mg (Table 2).¹¹³

12
13 The safety and efficacy of tirzepatide as treatment for obesity in people without diabetes has
14 been assessed at the recently published SURMOUNT-1 clinical trial. The study found that
15 tirzepatide 5-15mg together with a moderate intensity lifestyle intervention for 72 weeks resulted
16 in 30-57% of participants achieving $\geq 20\%$ WL and 15-36% $\geq 25\%$ WL compared to 3% and
17 1.5% with placebo respectively.¹⁰⁵ The physical function was improved more with tirzepatide
18 compared to placebo at the SURMOUNT-1 study and the mean reduction in total body fat mass
19 was 33.9% with tirzepatide compared to 8.2% with placebo.¹⁰⁵ Between participants with
20 prediabetes, 95.3% had reverted to normoglycaemia in the tirzepatide group at 72 weeks, as
21 compared with 61.9% of participants in the placebo group.¹⁰⁵

1 Nausea, diarrhea, vomiting and constipation were the most commonly reported side effects both
2 in SURPASS programme and in SURMOUNT-1 study. Most of them were minor to moderate in
3 severity and temporary. Tirzepatide did not increase the risk of hypoglycemia in SURPASS
4 programme unless it was combined with insulin or sulfonylureas.^{14, 118, 119} Decreased appetite
5 was also a commonly reported side effect. Adverse events leading to discontinuation of
6 medication ranged from 3-11% with tirzepatide 5mg to 7-11% with tirzepatide 15mg at
7 SURPASS programme and between 4.3–7.1% at SURMOUNT-1.^{14, 105, 113, 117-119} In
8 SURMOUNT-1, the incidence of pancreatitis was low and similar between tirzepatide and
9 placebo group (0.2% in each group), when cholecystitis was reported more frequently with
10 tirzepatide compared to placebo (the overall incidence was still low, <0.6%), possibly due to the
11 considerable weight reduction with the medication.¹⁰⁵

12 Cardiometabolic risk factors (SBP, total cholesterol, HDL and LDL) are all improved with
13 tirzepatide in people with and without T2D.^{14, 105, 118} In SURPASS-4 study, people with T2D and
14 increased cardiovascular risk were randomized to tirzepatide 5-15 mg (997 participants) or
15 insulin glargine (1005 participants) for at least 52 weeks, with treatment continued for a
16 maximum of 104 weeks aiming to provide some initial evidence on cardiovascular safety of
17 tirzepatide.¹¹⁸ An adjudicated 4-point MACE (cardiovascular death, myocardial infarction,
18 stroke, hospitalisation for unstable angina) occurred in 109 participants and was not increased on
19 tirzepatide compared with glargine (HR 0.74, 95% CI 0.51-1.08).¹¹⁸ Additionally, a prespecified
20 cardiovascular meta-analysis including all seven randomized controlled trials from the
21 SURPASS programme compared the time to first occurrence of a 4-point MACE (cardiovascular
22 death, myocardial infarction, stroke and hospitalized unstable angina) between pooled tirzepatide
23 groups and control groups.¹²⁰ Overall, 142 participants (109 from the SURPASS-4 study) had at

1 least one MACE-4 event. The hazard ratios comparing tirzepatide versus controls were 0.80
2 (95% CI, 0.57–1.11) for MACE-4; 0.90 (95% CI, 0.50–1.61) for cardiovascular death; and 0.80
3 (95% CI, 0.51–1.25) for all-cause death.¹²⁰ These results suggest that that there is no excess
4 cardiovascular risk with tirzepatide, however the definite impact of tirzepatide on cardiovascular
5 disease in people with T2D will be addressed in the ongoing SURPASS-CVOT study
6 (NCT04255433). The impact of tirzepatide in people with heart failure with preserved ejection
7 fraction and obesity will also be assessed at the SUMMIT trial (NCT04847557).

8
9 Overall, the GLP-1/GIP co-agonist tirzepatide, is the first approved treatment for T2D which at
10 the higher dose (15mg) consistently leads to >10% mean WL in studies with at least 52 weeks
11 follow-up (Table 2), despite that at the SURPASS programme there was no additional lifestyle
12 intervention. Moreover, in people with obesity (without diabetes) tirzepatide 10mg and 15mg
13 when combined with moderate intensity lifestyle interventions can lead to ≈20% mean WL with
14 good tolerability and similar side effect profile to that of GLP-1 RAs.

16 **4. A new era in obesity pharmacotherapy**

17 The WL achieved with semaglutide 2.4mg in people with obesity and the dual agonist tirzepatide
18 in people with T2D and/or obesity suggests that we are entering a new era in obesity
19 pharmacotherapy where ≥15% WL and maintenance is feasible (Figure 3A and Figure 3B).

20 These obesity treatments will be presented to patients only if the healthcare providers understand
21 that obesity is a chronic disease which is difficult to treat with lifestyle changes alone and the
22 management usually requires a multimodal treatment strategy including pharmacotherapy.⁹⁸

1 Both clinicians and public or private payers need to understand that sustained WL requires
2 lifelong treatment of obesity as otherwise weight regain will occur when treatment is
3 discontinued.⁴⁴ There are however important research priorities over the next years to allow the
4 new obesity pharmacotherapies to become more widely acceptable and available.

5

6 **4.1 The cardiovascular safety of new pharmacotherapies for obesity**

7 In the past, multiple WL medications have been withdrawn due to safety concerns.⁵⁶⁻⁵⁸ Today,
8 good quality evidence is lacking regarding the cardiovascular benefits of the approved
9 pharmacotherapies for obesity as discussed before, although the results of the cardiovascular
10 outcome trials conducted in people with T2D are likely to also apply to people with obesity.
11 Currently, the SELECT study is taking place and will assess the effect of semaglutide 2.4mg on
12 cardiovascular outcomes in people with obesity and established cardiovascular disease but
13 without diabetes. Moreover, SURPASS-CVOT study will compare dulaglutide vs tirzepatide on
14 cardiovascular outcomes in people with T2D and established cardiovascular disease and will
15 provide evidence on whether the dual GLP-1/GIP co-agonist is as safe as GLP-1 RAs. Future
16 studies will be needed to establish the safety and benefits of the new medications, including the
17 new combinations of gut hormones.

18

19

1 **4.2 How we can best combine the new pharmacotherapies with lifestyle interventions to**
2 **achieve weight loss targets and healthy weight maintenance?**

3 The majority of the clinical trials combine pharmacotherapies for obesity with moderate intensity
4 lifestyle changes. However, intensive lifestyle interventions including low calorie diets and
5 structured exercise may be used to support WL in clinical practice. How to best combine an
6 intensive lifestyle intervention with pharmacotherapies for obesity treatment requires further
7 investigation.

8 A single-centre clinical trial assessed the efficacy in weight maintenance of liraglutide 3mg
9 and/or a 52 week structured exercise programme versus placebo and continuing with usual
10 physical activity, in people who achieved at least 5% WL through an 8-week low calorie diet
11 (“responders” to low calorie diet).²¹ The combination of liraglutide 3mg with a structured
12 exercise programme (n=49) resulted in 15.7% mean total WL at 60 weeks after initiation of the
13 low calorie diet with 49% of participants achieving $\geq 15\%$ WL and 32% achieving $\geq 20\%$ WL.²¹
14 In participants receiving placebo and continuing with usual activity (n=49) after at least 5% WL
15 with the 8-week low calorie diet, mean WL at 60 weeks was 6.2% and only 10% of participants
16 were able to achieve $\geq 15\%$ WL.²¹ Importantly, the addition of the exercise programme also
17 caused a greater loss of fat mass, preservation of lean mass, improved cardiorespiratory fitness
18 and overall improvement in cardiometabolic risk factors compared with the WL obtained with
19 liraglutide 3mg alone.²¹ The WL achieved in this trial (at 60 weeks) with the combination of
20 liraglutide 3mg plus structured exercise for weight maintenance in people who were
21 “responders” to the initial 8-week low calorie diet is similar to the WL reported with semaglutide
22 2.4mg once weekly at 68 weeks when combined with a 500 kcal deficit diet¹⁵ (STEP-1 study,

1 Table 1) and significantly more than the 8% WL in SCALE-Obesity where liraglutide 3mg was
2 combined with 500 kcal deficit diet and advise for physical activity (Table 1).⁸⁴

3 On the other hand, in the STEP-3 study where semaglutide 2.4mg was combined with IBT and
4 an 8-week low calorie diet,^{15, 96} the WL achieved at 68 weeks was similar to the WL reported
5 when Semaglutide 2.4mg was combined with a 500kcal/day deficit diet¹⁵ (16% vs 14.9%) and
6 less when compared with patients who could tolerate Semaglutide 2.4mg in the STEP 4 study
7 (16% vs 17.4%).¹⁰⁰ These results suggest the possibility that intensive lifestyle treatments may
8 not be able to provide additional WL to effective obesity medications such as semaglutide and
9 tirzepatide. However, lean muscle mass loss remains a challenge, because with effective obesity
10 treatments patients consume small amount of calories and may not be enough space in their diet
11 to ensure adequate protein intake, thus rendering them catabolic and burning muscle mass. The
12 addition of exercise to these effective pharmacological interventions may further improve body
13 composition, physical function and cardiorespiratory fitness.²¹ Further studies are necessary to
14 help us understand how to best combine the new pharmacotherapies with different lifestyle
15 interventions not only to maximise WL, but also to optimise body composition and health
16 benefits.

17 Moreover, the sustainability of WL achieved through different combinations of intensive
18 lifestyle and pharmacotherapy needs to be assessed with long-term studies, together with the
19 changes in body composition, appetite and energy expenditure over time.

20

21

1 **4.3 The long-term clinical effectiveness and cost-effectiveness of new pharmacotherapies**

2 Similar to treatments for other chronic diseases such as hypertension or diabetes, at the moment
3 that the treatment for obesity stops the disease will relapse and body weight will increase again,
4 as was seen in the STEP 1 extension study.⁴⁴ In this exploratory analysis, a representative subset
5 of participants (n=327) who completed 68 weeks of treatment with semaglutide 2.4mg in STEP-
6 1 trial and achieved mean WL of 17.3% of their baseline weight, underwent an off-treatment
7 extension (including lifestyle intervention) for an additional year.⁴⁴ One year after withdrawal of
8 semaglutide 2.4 mg and lifestyle intervention, participants regained two-thirds of their prior WL
9 resulting in final total WL of 5.6% from baseline weight.⁴⁴ Cardiometabolic improvements seen
10 with semaglutide treatment were also reverted towards baseline at the end of the off-treatment
11 extension period for most parameters.⁴⁴

12 Additionally, in the STEP-4 trial, adults who were overweight or had obesity completed a 20-
13 week run-in of weekly treatment with subcutaneous semaglutide, 2.4 mg, with a mean WL of
14 10.6%, and then were randomized to continued treatment with subcutaneous semaglutide vs
15 placebo for an additional 48 weeks.¹⁰⁰ At the end of the trial, people receiving semaglutide
16 2.4mg lost a further 7.9% of their body weight whereas those on placebo regained 6.9% of their
17 body weight (almost 70% of the weight lost).¹⁰⁰

18 These results suggest that ongoing treatment is required to maintain improvements in weight,
19 although this topic so far has been poorly explored. Perhaps, an initial WL could be maintained
20 long-term with lower doses of anti-obesity medications. For example, 1.2mg liraglutide was
21 sufficient to maintain WL for a year after an initial 12% WL obtained with a low calorie diet¹²¹.

1 Currently, there is a lack of long-term data on the effectiveness and safety of obesity
2 pharmacotherapies and on the improvement in obesity-related comorbidities (so far the longest
3 follow-up study is for liraglutide 3mg up to 3 years after initiation of treatment).⁸⁸ The release of
4 the STEP-5 study results (presented but not published yet) demonstrate that 104 weeks of
5 semaglutide 2.4mg once weekly results in 15.2% WL compared to 2.6% with placebo, with
6 36.1% of participants in semaglutide group achieving $\geq 20\%$ WL at the end of the study.¹²²
7 Studies in real world settings with long-term follow-up on the new obesity pharmacotherapies
8 may also provide detailed information about the cost-effectiveness of these interventions and
9 may facilitate their approval by public and private payers for long-term use. Long-term data will
10 provide additional information on the potential long-term side effects of obesity
11 pharmacotherapy including adverse events due to significant long-term WL. Weight loss through
12 bariatric surgery has been associated with increased risk for fractures¹²³ and increased risk of
13 self-harm behaviors¹²⁴ – whether these complications will be observed with the new
14 pharmacotherapies need further investigation.

15
16 In summary, further evidence on the long-term safety (especially cardiovascular safety), clinical
17 effectiveness and cost-effectiveness of the new pharmacotherapies for obesity in real-world
18 settings will support their wider use and acceptability by healthcare professionals, individuals
19 living with obesity and healthcare systems.

20

1

2 **5. Other gut hormones in the pipeline as potential future therapeutic candidates**

3 **5.1 Amylin analogues**

4 Amylin is a pancreatic β -cell hormone that is co-secreted with insulin in response to food
5 intake.¹²⁵ It functions as a satiety signal, acting upon brain regions involved in both homeostatic
6 and hedonic appetite regulation; it also slows the gastric emptying, and thereby suppresses
7 postprandial glucagon responses to meals.¹²⁵

8 Cagrilintide is a weekly subcutaneous amylin analogue that is under development as treatment
9 for obesity. In a phase 2 study, people with obesity were randomly assigned to cagrilintide 0.3–
10 4.5 mg, liraglutide 3.0 mg, or placebo for 26 weeks.¹⁰⁶ Cagrilintide led to dose-dependent weight
11 reductions and greater WL at all doses compared to placebo at 26 weeks.¹⁰⁶ Weight loss with
12 cagrilintide 4.5 mg (10.8%) was greater than with liraglutide 3.0 mg (9.0%) or placebo (3.0%).¹⁰⁶
13 Cagrilintide 4.5 mg resulted in $\geq 10\%$ WL in 53.5% of participants and $\geq 15\%$ weight loss in
14 18.7% of participants.¹⁰⁶ Gastrointestinal disorders were the most common adverse events,
15 primarily nausea.¹⁰⁶

16 Different doses of cagrilintide were also evaluated in a phase 1b study in combination with
17 semaglutide 2.4 mg. At 20 weeks, cagrilintide 2.4 mg and semaglutide 2.4 mg led to 17.1% WL
18 compared with 9.8% loss with semaglutide 2.4 mg plus placebo.¹²⁶ This increased WL was not
19 accompanied by worsening tolerability, suggesting that the two apparently complementary
20 mechanisms of action may be combined for potential additive WL. Further clinical trials
21 assessing the safety and efficacy of the combination of semaglutide plus cagrilintide as treatment
22 of obesity are expected to take place over next years.

1

2 **5.2 Glucagon agonists**

3 Glucagon is a 29-amino acid peptide that is secreted from pancreatic α -cells in response to low
4 levels of blood glucose or increasing levels of amino acids. It increases blood glucose through
5 stimulation of glycogenolysis in the liver, but it also reduces food intake, increases satiety and
6 possibly energy expenditure.¹²⁷

7 The concept of GLP-1/glucagon co-agonists includes the concurrent activation of the GLP-1
8 receptors leading to decreased energy intake and the glucagon receptors causing increased
9 energy expenditure and reduced energy intake. Animal studies with potent GLP-1/glucagon co-
10 agonists were promising, however the results of the clinical studies in humans for the dual GLP-
11 1/glucagon receptor agonist cotadutide, currently under development, were less impressive.^{107, 128}

12 In a phase 2b, randomized, double-blind study, adults who were overweight or had obesity with
13 T2D were randomized to receive cotadutide 100 μ g, 200 μ g, or 300 μ g; placebo; or open-label
14 liraglutide 1.8 mg for 54 weeks.¹⁰⁷ The body weight reduction with cotadutide 300 μ g was 5.02%
15 at week 54 (compared to -0.68% in placebo group and -3.33% with liraglutide 1.8mg) and 15.5%
16 of people on cotadutide 300 μ g achieved $\geq 10\%$ WL. Cotadutide also significantly lowered
17 HbA_{1c} by 1.03 - 1.19% at week 54 while reduction with placebo was 0.45% and 1.17% with
18 liraglutide 1.8mg.¹⁰⁷ Gastrointestinal disorders, including diarrhoea, nausea, and vomiting, were
19 the most commonly reported adverse events with cotadutide at any tested dose and more patients
20 stopped cotadutide due to side effects compared to placebo or liraglutide 1.8mg.¹⁰⁷ However,
21 glucagon is also thought to increase hepatic lipid oxidation and inhibit lipogenesis and ad hoc

1 analysis of this trial with cotatutide demonstrated improvements in hepatic parameters and
2 supports further evaluation of cotadutide in nonalcoholic steatohepatitis (NASH).¹⁰⁷

3 Another GLP-1/glucagon receptor dual agonist (SAR425899) was recently evaluated in single-
4 ascending dose and multiple-ascending dose phase 1 trials where it was given once a day over
5 28 days.¹²⁹ At the highest maintenance doses tested, there was a reduction of HbA1c by 0.54-
6 0.59% when given to patients who were overweight or had obesity with T2D, and mean WL of
7 2.4-5.5 kg over the 28 days.¹²⁹ SAR425899 was generally well tolerated, with treatment-
8 emergent adverse effects of reduced appetite and nausea.¹²⁹

9
10 Regarding triple agonists, evidence from experimental studies in animals suggest that the
11 addition of GIP activity into dual GLP-1 and glucagon receptor agonism provides improved
12 weight loss and glycemic control while protecting against the diabetogenic risk of chronic
13 glucagon agonism.^{129, 130} Importantly, the addition of the GIP component may allow an increased
14 potency of the agonist at the glucagon receptor. However, very limited data is available from
15 clinical trials - a phase 1 clinical study in healthy individuals (lean to overweight) with a new
16 unimolecular GLP-1, GIP, and glucagon receptor triagonist (SAR441255) showed that the
17 triagonist improved glycaemic control during a mixed-meal tolerance test and was well
18 tolerated.¹³⁰ Additionally, a recent abstract presented the results of a 12-week, phase 1 study,
19 where the safety and tolerability of multiple doses of another GLP-1/GIP/glucagon co-agonist
20 (LY3437943) compared to placebo were assessed in 72 people with T2D. The triple co-agonist
21 showed similar safety and tolerability profile to other incretins and led to placebo-adjusted
22 reduction in HbA1C of up to 1.56% and to placebo-adjusted weight reduction of up to 8.96 kg.¹³¹

1 Further trials in larger populations of people with T2D and obesity are required to confirm the
2 therapeutic potential of GLP-1/GIP/glucagon receptor triagonists.

3

4 **5.3 PYY analogues**

5 PYY is a peptide hormone that is co-secreted with GLP-1, particularly from distal epithelial L
6 cells in the gut in response to food intake. PYY3-36 is the active form of the peptide and acts as
7 a satiety hormone, suppressing food intake via activation of Y2 receptors in the hypothalamus.
8 Infusion of PYY3-36 in people with obesity causes a 30% reduction in food intake.¹³² A recent
9 phase 1 study investigating a long-acting PYY3-36 analogue demonstrates a reduction of 38-
10 55% in food intake vs placebo at 30 days after initiation of treatment and WL of 2.87kg – 3.58kg
11 compared to placebo.¹³³

12 The coadministration of GLP-1 and PYY3-36 in humans also reduced energy intake compared
13 with placebo and more than the sum of the individual infusions, demonstrating a synergistic
14 effect.^{134, 135} A long-acting PYY analogue in combination with semaglutide is now being
15 assessed in a phase 2 study as treatment for obesity (NCT04969939).

16

17 **5.4 Summary of potential future obesity treatments based on gut hormones**

18 Except of the approved GLP-1 RAs for weight management and the GLP-1/GIP co-agonist
19 tirzeparide which has completed phase 3 trials as treatment for T2D and/or obesity, multiple
20 other gut hormones such as amylin, glucagon and PYY are being tested in early phase clinical
21 trials as potential treatments for obesity and obesity-related complications, either as

1 monotherapies (amylin, PYY) or in combination with GLP-1 as dual (GLP-1/amylin, GLP-
2 1/PYY, GLP-1/glucagon) and triple co-agonists (GLP-1/GIP/glucagon). A phase 3 trial assessing
3 the efficacy and safety of the combination of semaglutide 2.4mg with cagrilintide 2.4mg once
4 weekly for people with obesity and T2D is expected to start at the last trimester of 2022
5 (REDEFINE 2, NCT05394519). In the near future, there is a real prospect of the above described
6 gut hormone combinations to deliver improved weight-related outcomes over the currently
7 available treatments for obesity and T2D.

8

9 **6. Obesity treatments not based on gut hormones**

10 It is common practice in chronic diseases such as hypertension or diabetes to target multiple
11 mechanisms to achieve optimal disease management. Similarly, in obesity, despite that research
12 has mainly focused in combinations of gut hormones, new treatments targeting different
13 pathways such as Setmelanotide and Bimagrumb have also been developed.

14 Setmelanotide is an melanocortin-4 Receptor (MC4R) agonist that reduces bodyweight and
15 hunger in individuals with ultra-rare obesity genetic disorders caused by leptin receptor (LEPR)
16 or pro-opiomelanocortin (POMC) deficiency (80% of participants in POMC trial and 45% of
17 participants in LEPR trial achieved at least 10% WL after 1 year of medication use).¹³⁶

18 Individuals with these genetic variants have severe hunger (hyperphagia) and early-onset severe
19 obesity resulting from disruption at the melanocortin pathway, which plays pivotal part in body
20 weight regulation.¹³⁶ Setmelanotide has now been approved in the US and Europe for chronic
21 weight management in patients 6 years and older with obesity resulting from POMC, PCSK1 or
22 LEPR deficiency confirmed by genetic testing.

1 Bimagrumab is a fully human monoclonal antibody that binds the activin type 2 receptors and
2 prevents the actions of natural ligands, including myostatin and activin A, that otherwise
3 negatively regulate skeletal muscle growth.^{137, 138} In phase 2 clinical trials, 48 weeks of treatment
4 with Bimagrumab in individuals living with obesity and T2D resulted in WL of 6.5% compared
5 to 0.5% (-0.18 kg) in the placebo group, with a reduction in total body fat mass by 20.5% (-7.49
6 kg) and an increase in the lean mass by 3.6%, suggesting that Bimagrumab could be a potential
7 treatment for sarcopenic obesity. HbA1c fell by 0.76% compared to a rise by 0.04% with
8 placebo.¹³⁷ Dietary intake based on 24-h recall did not differ from baseline at the end of the
9 study, suggesting that increase in energy expenditure could be a mechanism of action for the WL
10 with this medication.¹³⁷

11

12 Overall, Setmelanotide is considered the first approved personalised treatment for obesity (for
13 individuals with confirmed ultra-rare obesity genetic disorders) when the early phase trials with
14 Bimagrumab provide evidence that we may succeed in improving the quality of weight loss and
15 preserve lean mass in the treatment of obesity.

16

17 **7. Conclusion**

18 WL $\geq 10\%$ and maintenance is challenging with lifestyle changes alone due to compensatory
19 increases in appetite and reduction in energy expenditure. Bariatric surgery is currently the most
20 effective intervention for sustained WL $\geq 20\%$ and leads to multiple health benefits, but surgical
21 procedures are difficult to scale to treat the entire population. Over the last decade, a number of
22 medications have been approved for chronic weight management in people with obesity but

1 Semaglutide 2.4mg once weekly (a new GLP-1 RA) is the first one which leads to $\approx 15\%$ WL (in
2 people without diabetes). Moreover, the WL achieved in people with T2D and/or obesity at
3 phase 3 clinical trials with the recently approved for T2D management dual agonist tirzepatide
4 suggests that combination of gut hormones may lead to additional WL compared to GLP-1 RAs
5 alone. Judging from the results of clinical trials in individuals with T2D, these treatments may
6 also have beneficial cardiovascular effects. Additional research assessing long-term safety,
7 effectiveness and cost-effectiveness of these new pharmacotherapies (semaglutide 2.4mg and
8 tirzepatide) in trials and real-world settings will help us to understand better their position in the
9 weight management algorithms for people with obesity and/or T2D. Furthermore, novel
10 pharmacological interventions combining GLP-1 with other gut hormones are currently under
11 development and may offer in the future the potential to bridge further the efficacy gap between
12 bariatric surgery and the currently available pharmacotherapies.

14 **Funding:**

15 This work was supported by the Leicester NIHR Biomedical Research Centre. D.P. is funded
16 through an National Institute of Clinical Research Clinical Lectureship.

18 **Conflict of interest:**

19 D.P. has received grants from Novo Nordisk, Novo Nordisk UK Research Foundation, Academy
20 of Medical Sciences/ Diabetes UK and Health Education East Midlands. C.W.I.R. reports grants
21 from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research

1 Board. He serves on the advisory boards of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly,
2 Johnson & Johnson, Sanofi Aventis, AstraZeneca, Janssen, Bristol-Myers Squibb, Glia, and
3 Boehringer Ingelheim. C.W.I.R. is a member of the Irish Society for Nutrition and Metabolism
4 outside the area of work commented on here. He is the chief medical officer and director of the
5 Medical Device Division of Keyron since January, 2011. Both of these are unremunerated
6 positions. C.W.I.R. was a previous investor in Keyron, which develops endoscopically
7 implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy
8 and gastric bypass. The product has only been tested in rodents and none of Keyron's products
9 are currently licensed. They do not have any contracts with other companies to put their products
10 into clinical practice. No patients have been included in any of Keyron's studies and they are not
11 listed on the stock market. C.W.I.R. was gifted stock holdings in September, 2021 and divested
12 all stock holdings in Keyron in September, 2021. He continues to provide scientific advice to
13 Keyron for no remuneration. J.J.H. is a member of advisory boards for Novo Nordisk and has
14 acted as a speaker for Novo Nordisk and Lilly. M.J.D. has acted as consultant, advisory board
15 member and speaker for Boehringer Ingelheim, Lilly, Novo Nordisk and Sanofi, an advisory
16 board member and speaker for AstraZeneca, an advisory board member for Janssen, Lexicon,
17 Pfizer and ShouTi Pharma Inc, a speaker for Napp Pharmaceuticals, Novartis and Takeda
18 Pharmaceuticals International Inc. and has received grants in support of investigator and
19 investigator initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim,
20 Astrazeneca and Janssen.

21

22

1 Data availability statement:

2 Data derived from sources in the public domain. Reference details are provided in full.

3

4 References

- 5 1. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A
6 position statement of the World Obesity Federation. *Obes Rev* 2017;**18**:715-723.
- 7 2. (WHO) WHO. Obesity and Overweight.
- 8 3. Haslam DW, James WP. Obesity. *Lancet* 2005;**366**:1197-1209.
- 9 4. Biener A, Cawley J, Meyerhoefer C. The High and Rising Costs of Obesity to the US Health Care
10 System. *J Gen Intern Med* 2017;**32**:6-8.
- 11 5. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *Jama*
12 2003;**289**:187-193.
- 13 6. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto
14 R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57
15 prospective studies. *Lancet* 2009;**373**:1083-1096.
- 16 7. Cawley J, Biener A, Meyerhoefer C, Ding Y, Zvenyach T, Smolarz BG, Ramasamy A. Direct medical
17 costs of obesity in the United States and the most populous states. *J Manag Care Spec Pharm*
18 2021;**27**:354-366.
- 19 8. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity*
20 (*Silver Spring*) 2014;**22**:5-13.
- 21 9. Tahrani AA, Morton J. Benefits of weight loss of 10% or more in patients with overweight or
22 obesity: A review. *Obesity (Silver Spring)* 2022;**30**:802-840.
- 23 10. Cefalu WT, Bray GA, Home PD, Garvey WT, Klein S, Pi-Sunyer FX, Hu FB, Raz I, Van Gaal L, Wolfe
24 BM, Ryan DH. Advances in the Science, Treatment, and Prevention of the Disease of Obesity:
25 Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care* 2015;**38**:1567-1582.
- 26 11. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective
27 controlled intervention study of bariatric surgery. *J Intern Med* 2013;**273**:219-234.
- 28 12. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard
29 C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK,
30 Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM. Effects of bariatric
31 surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;**357**:741-752.
- 32 13. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B,
33 Narbro K, Sjöström CD, Sullivan M, Wedel H. Lifestyle, diabetes, and cardiovascular risk factors
34 10 years after bariatric surgery. *N Engl J Med* 2004;**351**:2683-2693.
- 35 14. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, Mao H, Cui X, Karanikas
36 CA, Thieu VT. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in
37 patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet*
38 2021;**398**:143-155.
- 39 15. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM,
40 Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF. Once-
41 Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med* 2021;**384**:989.
- 42 16. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S,
43 Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Snihotta FF, Mathers

- 1 JC, Ross HM, McIlvenna Y, Welsh P, Kean S, Ford I, McConnachie A, Messow CM, Sattar N, Taylor
2 R. Durability of a primary care-led weight-management intervention for remission of type 2
3 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes*
4 *Endocrinol* 2019;**7**:344-355.
- 5 17. Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, Williamson D, Berkowitz RI, Kelley DE,
6 Tomchee C, Hill JO, Kumanyika S. The Look AHEAD study: a description of the lifestyle
7 intervention and the evidence supporting it. *Obesity (Silver Spring)* 2006;**14**:737-752.
- 8 18. Astbury NM, Aveyard P, Nickless A, Hood K, Corfield K, Lowe R, Jebb SA. Doctor Referral of
9 Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic
10 randomised controlled trial. *Bmj* 2018;**362**:k3760.
- 11 19. Astbury NM, Edwards RM, Ghebretinsea F, Shanyinde M, Mollison J, Aveyard P, Jebb SA.
12 Extended follow-up of a short total diet replacement programme: results of the Doctor Referral
13 of Overweight People to Low Energy total diet replacement Treatment (DROPLET) randomised
14 controlled trial at 3 years. *Int J Obes (Lond)* 2021;**45**:2432-2438.
- 15 20. Bellicha A, van Baak MA, Battista F, Beaulieu K, Blundell JE, Busetto L, Carraça EV, Dicker D,
16 Encantado J, Ermolao A, Farpour-Lambert N, Pramono A, Woodward E, Oppert JM. Effect of
17 exercise training on weight loss, body composition changes, and weight maintenance in adults
18 with overweight or obesity: An overview of 12 systematic reviews and 149 studies. *Obes Rev*
19 2021;**22 Suppl 4**:e13256.
- 20 21. Lundgren JR, Janus C, Jensen SBK, Juhl CR, Olsen LM, Christensen RM, Svane MS, Bandholm T,
21 Bojsen-Møller KN, Blond MB, Jensen JB, Stallknecht BM, Holst JJ, Madsbad S, Torekov SS.
22 Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined. *N Engl J Med*
23 2021;**384**:1719-1730.
- 24 22. Unick JL, Gaussoin SA, Hill JO, Jakicic JM, Bond DS, Hellgren M, Johnson KC, Peters AL, Coday M,
25 Kitzman DW, Bossart S, Wing RR. Four-Year Physical Activity Levels among Intervention
26 Participants with Type 2 Diabetes. *Med Sci Sports Exerc* 2016;**48**:2437-2445.
- 27 23. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, Kahn SE, Knowler WC,
28 Yanovski SZ. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial
29 of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials*
30 2003;**24**:610-628.
- 31 24. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM,
32 Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton
33 ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE,
34 Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall
35 H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht
36 LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle
37 intervention in type 2 diabetes. *N Engl J Med* 2013;**369**:145-154.
- 38 25. Pandey A, Patel KV, Bahnson JL, Gaussoin SA, Martin CK, Balasubramanyam A, Johnson KC,
39 McGuire DK, Bertoni AG, Kitzman D, Berry JD. Association of Intensive Lifestyle Intervention,
40 Fitness, and Body Mass Index With Risk of Heart Failure in Overweight or Obese Adults With
41 Type 2 Diabetes Mellitus: An Analysis From the Look AHEAD Trial. *Circulation* 2020;**141**:1295-
42 1306.
- 43 26. Alonso A, Bahnson JL, Gaussoin SA, Bertoni AG, Johnson KC, Lewis CE, Vetter M, Mantzoros CS,
44 Jeffery RW, Soliman EZ. Effect of an intensive lifestyle intervention on atrial fibrillation risk in
45 individuals with type 2 diabetes: the Look AHEAD randomized trial. *Am Heart J* 2015;**170**:770-
46 777.e775.
- 47 27. Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C,
48 Evans M, Foreyt J, Foster G, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jeffery RW, Johnson KC,

- 1 Kitabchi AE, Knowler WC, Kriska A, Lang W, Lewis CE, Montez MG, Nathan DM, Neiberg RH,
 2 Patricio J, Peters A, Pi-Sunyer X, Pownall H, Redmon B, Regensteiner J, Rejeski J, Ribisl PM,
 3 Safford M, Stewart K, Trencle D, Wadden TA, Wing RR, Yanovski SZ. Association of the magnitude
 4 of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in
 5 overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD
 6 randomised clinical trial. *Lancet Diabetes Endocrinol* 2016;**4**:913-921.
- 7 28. Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, Twomey D, Gallagher
 8 C, Hendriks JML, Linz D, McEvoy RD, Abhayaratna WP, Kalman JM, Lau DH, Sanders P.
 9 PREVENTion and regRESSive Effect of weight-loss and risk factor modification on Atrial
 10 Fibrillation: the REVERSE-AF study. *Europace* 2018;**20**:1929-1935.
- 11 29. Hall KD, Kahan S. Maintenance of Lost Weight and Long-Term Management of Obesity. *Med Clin*
 12 *North Am* 2018;**102**:183-197.
- 13 30. Aronne LJ, Hall KD, J MJ, Leibel RL, Lowe MR, Rosenbaum M, Klein S. Describing the Weight-
 14 Reduced State: Physiology, Behavior, and Interventions. *Obesity (Silver Spring)* 2021;**29 Suppl**
 15 **1**:S9-s24.
- 16 31. Busetto L, Bettini S, Makaronidis J, Roberts CA, Halford JCG, Batterham RL. Mechanisms of
 17 weight regain. *Eur J Intern Med* 2021;**93**:3-7.
- 18 32. Polidori D, Sanghvi A, Seeley RJ, Hall KD. How Strongly Does Appetite Counter Weight Loss?
 19 Quantification of the Feedback Control of Human Energy Intake. *Obesity (Silver Spring)*
 20 2016;**24**:2289-2295.
- 21 33. Ravussin E, Smith SR, Ferrante AW, Jr. Physiology of Energy Expenditure in the Weight-Reduced
 22 State. *Obesity (Silver Spring)* 2021;**29 Suppl 1**:S31-s38.
- 23 34. Fothergill E, Guo J, Howard L, Kerns JC, Knuth ND, Brychta R, Chen KY, Skarulis MC, Walter M,
 24 Walter PJ, Hall KD. Persistent metabolic adaptation 6 years after "The Biggest Loser"
 25 competition. *Obesity (Silver Spring)* 2016;**24**:1612-1619.
- 26 35. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, Proietto J. Long-term
 27 persistence of hormonal adaptations to weight loss. *N Engl J Med* 2011;**365**:1597-1604.
- 28 36. Dorling J, Broom DR, Burns SF, Clayton DJ, Deighton K, James LJ, King JA, Miyashita M, Thackray
 29 AE, Batterham RL, Stensel DJ. Acute and Chronic Effects of Exercise on Appetite, Energy Intake,
 30 and Appetite-Related Hormones: The Modulating Effect of Adiposity, Sex, and Habitual Physical
 31 Activity. *Nutrients* 2018;**10**.
- 32 37. Douglas JA, King JA, Clayton DJ, Jackson AP, Sargeant JA, Thackray AE, Davies MJ, Stensel DJ.
 33 Acute effects of exercise on appetite, ad libitum energy intake and appetite-regulatory
 34 hormones in lean and overweight/obese men and women. *Int J Obes (Lond)* 2017;**41**:1737-1744.
- 35 38. Beaulieu K, Blundell JE, van Baak MA, Battista F, Busetto L, Carraça EV, Dicker D, Encantado J,
 36 Ermolao A, Farpour-Lambert N, Pramono A, Woodward E, Bellicha A, Oppert JM. Effect of
 37 exercise training interventions on energy intake and appetite control in adults with overweight
 38 or obesity: A systematic review and meta-analysis. *Obes Rev* 2021;**22 Suppl 4**:e13251.
- 39 39. Grannell A, Fallon F, Al-Najim W, le Roux C. Obesity and responsibility: Is it time to rethink
 40 agency? *Obes Rev* 2021;**22**:e13270.
- 41 40. Iepsen EW, Lundgren J, Holst JJ, Madsbad S, Torekov SS. Successful weight loss maintenance
 42 includes long-term increased meal responses of GLP-1 and PYY3-36. *Eur J Endocrinol*
 43 2016;**174**:775-784.
- 44 41. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, Aronne L. Weight maintenance
 45 and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE
 46 Maintenance randomized study. *Int J Obes (Lond)* 2013;**37**:1443-1451.

- 1 42. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D. The effect of semaglutide 2.4
2 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults
3 with obesity. *Diabetes Obes Metab* 2021;**23**:754-762.
- 4 43. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog
5 liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese,
6 non-diabetic adults. *Int J Obes (Lond)* 2014;**38**:784-793.
- 7 44. Wilding JP, Batterham RL, Davies M, Gaal LFV, Kandler K, Konakli K, Lingvay I, McGowan BM,
8 Kalayci Oral T, Rosenstock J, Wadden TA, Wharton S, Yokote K, Kushner RF. Weight regain and
9 cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes
10 Obes Metab* 2022.
- 11 45. le Roux CW, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenus A, Lönroth H, Fändriks L,
12 Ghatei MA, Bloom SR, Olbers T. Gut hormones as mediators of appetite and weight loss after
13 Roux-en-Y gastric bypass. *Ann Surg* 2007;**246**:780-785.
- 14 46. Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, Ahlin S, Anveden Å,
15 Bengtsson C, Bergmark G, Bouchard C, Carlsson B, Dahlgren S, Karlsson J, Lindroos AK, Lönroth
16 H, Narbro K, Näslund I, Olbers T, Svensson PA, Carlsson LM. Bariatric surgery and long-term
17 cardiovascular events. *Jama* 2012;**307**:56-65.
- 18 47. Carlsson LMS, Sjöholm K, Jacobson P, Andersson-Assarsson JC, Svensson PA, Taube M, Carlsson
19 B, Peltonen M. Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study. *N
20 Engl J Med* 2020;**383**:1535-1543.
- 21 48. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjöström L, Karason K. Bariatric Surgery and the
22 Risk of New-Onset Atrial Fibrillation in Swedish Obese Subjects. *J Am Coll Cardiol* 2016;**68**:2497-
23 2504.
- 24 49. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Karason K. Surgical obesity treatment and the risk
25 of heart failure. *Eur Heart J* 2019;**40**:2131-2138.
- 26 50. Aminian A, Zajichek A, Arterburn DE, Wolski KE, Brethauer SA, Schauer PR, Kattan MW, Nissen
27 SE. Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients
28 With Type 2 Diabetes and Obesity. *Jama* 2019;**322**:1271-1282.
- 29 51. Eliasson B, Liakopoulos V, Franzén S, Näslund I, Svensson AM, Ottosson J, Gudbjörnsdottir S.
30 Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in
31 Sweden: a nationwide, matched, observational cohort study. *Lancet Diabetes Endocrinol*
32 2015;**3**:847-854.
- 33 52. Angrisani L, Santonicola A, Iovino P, Ramos A, Shikora S, Kow L. Bariatric Surgery Survey 2018:
34 Similarities and Disparities Among the 5 IFSO Chapters. *Obes Surg* 2021;**31**:1937-1948.
- 35 53. Arterburn D, Wellman R, Emiliano A, Smith SR, Odegaard AO, Murali S, Williams N, Coleman KJ,
36 Courcoulas A, Coley RY, Anau J, Pardee R, Toh S, Janning C, Cook A, Sturtevant J, Horgan C,
37 McTigue KM. Comparative Effectiveness and Safety of Bariatric Procedures for Weight Loss: A
38 PCORnet Cohort Study. *Ann Intern Med* 2018;**169**:741-750.
- 39 54. Miras AD, le Roux CW. Mechanisms underlying weight loss after bariatric surgery. *Nat Rev
40 Gastroenterol Hepatol* 2013;**10**:575-584.
- 41 55. Svane MS, Jørgensen NB, Bojsen-Møller KN, Dirksen C, Nielsen S, Kristiansen VB, Toräng S,
42 Wewer Albrechtsen NJ, Rehfeld JF, Hartmann B, Madsbad S, Holst JJ. Peptide YY and glucagon-
43 like peptide-1 contribute to decreased food intake after Roux-en-Y gastric bypass surgery. *Int J
44 Obes (Lond)* 2016;**40**:1699-1706.
- 45 56. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. Anti-obesity drug discovery: advances and
46 challenges. *Nat Rev Drug Discov* 2022;**21**:201-223.

- 1 57. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C,
2 Sharma AM, Shepherd GM, Rode RA, Renz CL. Effect of sibutramine on cardiovascular outcomes
3 in overweight and obese subjects. *N Engl J Med* 2010;**363**:905-917.
- 4 58. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-
5 loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 2007;**370**:1706-1713.
- 6 59. Sharretts J, Galescu O, Gomatam S, Andraca-Carrera E, Hampp C, Yanoff L. Cancer Risk
7 Associated with Lorcaserin - The FDA's Review of the CAMELLIA-TIMI 61 Trial. *N Engl J Med*
8 2020;**383**:1000-1002.
- 9 60. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, Loomba R, Camilleri M, Singh S.
10 Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A
11 Systematic Review and Meta-analysis. *Jama* 2016;**315**:2424-2434.
- 12 61. Smith SM, Meyer M, Trinkley KE. Phentermine/topiramate for the treatment of obesity. *Ann*
13 *Pharmacother* 2013;**47**:340-349.
- 14 62. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, Tam PY, Troupin B,
15 Day WW. Controlled-release phentermine/topiramate in severely obese adults: a randomized
16 controlled trial (EQUIP). *Obesity (Silver Spring)* 2012;**20**:330-342.
- 17 63. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW,
18 Bowden CH. Two-year sustained weight loss and metabolic benefits with controlled-release
19 phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-
20 controlled, phase 3 extension study. *Am J Clin Nutr* 2012;**95**:297-308.
- 21 64. Garvey WT, Ryan DH, Bohannon NJ, Kushner RF, Rueger M, Dvorak RV, Troupin B. Weight-loss
22 therapy in type 2 diabetes: effects of phentermine and topiramate extended release. *Diabetes*
23 *Care* 2014;**37**:3309-3316.
- 24 65. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, Day WW. Effects of low-
25 dose, controlled-release, phentermine plus topiramate combination on weight and associated
26 comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled,
27 phase 3 trial. *Lancet* 2011;**377**:1341-1352.
- 28 66. Kolotkin RL, Gadde KM, Peterson CA, Crosby RD. Health-related quality of life in two randomized
29 controlled trials of phentermine/topiramate for obesity: What mediates improvement? *Qual Life*
30 *Res* 2016;**25**:1237-1244.
- 31 67. Ritchey ME, Harding A, Hunter S, Peterson C, Sager PT, Kowey PR, Nguyen L, Thomas S, Cainzos-
32 Achirica M, Rothman KJ, Andrews EB, Anthony MS. Cardiovascular Safety During and After Use
33 of Phentermine and Topiramate. *J Clin Endocrinol Metab* 2019;**104**:513-522.
- 34 68. Apovian CM. Naltrexone/bupropion for the treatment of obesity and obesity with Type 2
35 diabetes. *Future Cardiol* 2016;**12**:129-138.
- 36 69. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, Kim DD,
37 Dunayevich E. Effect of naltrexone plus bupropion on weight loss in overweight and obese
38 adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.
39 *Lancet* 2010;**376**:595-605.
- 40 70. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, Kim D, Dunayevich E. A randomized,
41 phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II).
42 *Obesity (Silver Spring)* 2013;**21**:935-943.
- 43 71. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, Perri MG, Pi-Sunyer FX, Rock CL,
44 Erickson JS, Maier HN, Kim DD, Dunayevich E. Weight loss with naltrexone SR/bupropion SR
45 combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver*
46 *Spring)* 2011;**19**:110-120.
- 47 72. Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, Klassen P, Fujioka K. Effects
48 of naltrexone sustained-release/bupropion sustained-release combination therapy on body

- 1 weight and glycemic parameters in overweight and obese patients with type 2 diabetes.
2 *Diabetes Care* 2013;**36**:4022-4029.
- 3 73. Kolotkin RL, Chen S, Klassen P, Gilder K, Greenway FL. Patient-reported quality of life in a
4 randomized placebo-controlled trial of naltrexone/bupropion for obesity. *Clin Obes* 2015;**5**:237-
5 244.
- 6 74. Halseth A, Shan K, Gilder K, Malone M, Acevedo L, Fujioka K. Quality of life, binge eating and
7 sexual function in participants treated for obesity with sustained release naltrexone/bupropion.
8 *Obes Sci Pract* 2018;**4**:141-152.
- 9 75. Nissen SE, Wolski KE, Prcela L, Wadden T, Buse JB, Bakris G, Perez A, Smith SR. Effect of
10 Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese
11 Patients With Cardiovascular Risk Factors: A Randomized Clinical Trial. *Jama* 2016;**315**:990-1004.
- 12 76. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev* 2007;**87**:1409-1439.
- 13 77. Näslund E, Barkeling B, King N, Gutniak M, Blundell JE, Holst JJ, Rössner S, Hellström PM. Energy
14 intake and appetite are suppressed by glucagon-like peptide-1 (GLP-1) in obese men. *Int J Obes
15 Relat Metab Disord* 1999;**23**:304-311.
- 16 78. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses
17 energy intake in humans. *J Clin Invest* 1998;**101**:515-520.
- 18 79. Williams DL. The diverse effects of brain glucagon-like peptide 1 receptors on ingestive
19 behaviour. *Br J Pharmacol* 2022;**179**:571-583.
- 20 80. Sisley S, Gutierrez-Aguilar R, Scott M, D'Alessio DA, Sandoval DA, Seeley RJ. Neuronal GLP1R
21 mediates liraglutide's anorectic but not glucose-lowering effect. *J Clin Invest* 2014;**124**:2456-
22 2463.
- 23 81. Farr OM, Upadhyay J, Rutagengwa C, DiPrisco B, Ranta Z, Adra A, Bapatla N, Douglas VP, Douglas
24 KAA, Nolen-Doerr E, Mathew H, Mantzoros CS. Longer-term liraglutide administration at the
25 highest dose approved for obesity increases reward-related orbitofrontal cortex activation in
26 response to food cues: Implications for plateauing weight loss in response to anti-obesity
27 therapies. *Diabetes Obes Metab* 2019;**21**:2459-2464.
- 28 82. Holst JJ. Treatment of Type 2 Diabetes and Obesity on the Basis of the Incretin System: The 2021
29 Banting Medal for Scientific Achievement Award Lecture. *Diabetes* 2021;**70**:2468-2475.
- 30 83. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, Mastrandrea LD, Prabhu N,
31 Arslanian S. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. *N Engl J
32 Med* 2020;**382**:2117-2128.
- 33 84. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW,
34 Violante Ortiz R, Jensen CB, Wilding JP. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in
35 Weight Management. *N Engl J Med* 2015;**373**:11-22.
- 36 85. Wadden TA, Tronieri JS, Sugimoto D, Lund MT, Auerbach P, Jensen C, Rubino D. Liraglutide 3.0
37 mg and Intensive Behavioral Therapy (IBT) for Obesity in Primary Care: The SCALE IBT
38 Randomized Controlled Trial. *Obesity (Silver Spring)* 2020;**28**:529-536.
- 39 86. Garvey WT, Birkenfeld AL, Dicker D, Mingrone G, Pedersen SD, Satynganova A, Skovgaard D,
40 Sugimoto D, Jensen C, Mosenzon O. Efficacy and Safety of Liraglutide 3.0 mg in Individuals With
41 Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin
42 Randomized Controlled Trial. *Diabetes Care* 2020;**43**:1085-1093.
- 43 87. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, Andreasen AH, Jensen CB,
44 DeFronzo RA. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The
45 SCALE Diabetes Randomized Clinical Trial. *Jama* 2015;**314**:687-699.
- 46 88. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, Ortiz RV, Wilding JPH, Skjøth
47 TV, Manning LS, Pi-Sunyer X. 3 years of liraglutide versus placebo for type 2 diabetes risk

- 1 reduction and weight management in individuals with prediabetes: a randomised, double-blind
2 trial. *Lancet* 2017;**389**:1399-1409.
- 3 89. Kolotkin RL, Fujioka K, Wolden ML, Brett JH, Bjorner JB. Improvements in health-related quality
4 of life with liraglutide 3.0 mg compared with placebo in weight management. *Clin Obes*
5 2016;**6**:233-242.
- 6 90. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, Claudius B, Jensen CB,
7 Mignot E. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe
8 obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes (Lond)*
9 2016;**40**:1310-1319.
- 10 91. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock
11 S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB.
12 Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016;**375**:311-322.
- 13 92. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A, Nilsson B, Møller JE,
14 Hjort J, Rasmussen J, Boesgaard TW, Schou M, Videbaek L, Gustafsson I, Flyvbjerg A, Wiggers H,
15 Tarnow L. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in
16 stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-
17 blind, randomised, placebo-controlled trial. *Eur J Heart Fail* 2017;**19**:69-77.
- 18 93. Marso SP, Baeres FMM, Bain SC, Goldman B, Husain M, Nauck MA, Poulter NR, Pratley RE,
19 Thomsen AB, Buse JB. Effects of Liraglutide on Cardiovascular Outcomes in Patients With
20 Diabetes With or Without Heart Failure. *J Am Coll Cardiol* 2020;**75**:1128-1141.
- 21 94. Davies MJ, Aronne LJ, Caterson ID, Thomsen AB, Jacobsen PB, Marso SP. Liraglutide and
22 cardiovascular outcomes in adults with overweight or obesity: A post hoc analysis from SCALE
23 randomized controlled trials. *Diabetes Obes Metab* 2018;**20**:734-739.
- 24 95. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, Wadden TA, Wizert A,
25 Garvey WT. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in
26 Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial.
27 *Jama* 2022;**327**:138-150.
- 28 96. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino
29 DM, Skovgaard D, Wallenstein SOR, Garvey WT. Effect of Subcutaneous Semaglutide vs Placebo
30 as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or
31 Obesity: The STEP 3 Randomized Clinical Trial. *Jama* 2021;**325**:1403-1413.
- 32 97. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J,
33 Shimomura I, Viljoen A, Wadden TA, Lingvay I. Semaglutide 2.4 mg once a week in adults with
34 overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-
35 dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;**397**:971-984.
- 36 98. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal
37 for type 2 diabetes: time to reframe the conversation. *Lancet* 2022;**399**:394-405.
- 38 99. Wharton S, Calanna S, Davies M, Dicker D, Goldman B, Lingvay I, Mosenzon O, Rubino DM,
39 Thomsen M, Wadden TA, Pedersen SD. Gastrointestinal tolerability of once-weekly semaglutide
40 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal
41 adverse events and weight loss. *Diabetes Obes Metab* 2022;**24**:94-105.
- 42 100. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O,
43 Rosenstock J, Rubio MA, Rudofsky G, Tadayon S, Wadden TA, Dicker D. Effect of Continued
44 Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With
45 Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *Jama* 2021;**325**:1414-1425.
- 46 101. Kadowaki T, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, Tobe K, Yamauchi T, Lim S.
47 Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes

- 1 in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-
 2 controlled, phase 3a trial. *Lancet Diabetes Endocrinol* 2022;**10**:193-206.
- 3 102. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert
 4 J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T. Semaglutide and
 5 Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016;**375**:1834-1844.
- 6 103. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of Oral
 7 Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in
 8 Patients With Type 2 Diabetes: A Randomized Clinical Trial. *Jama* 2017;**318**:1460-1470.
- 9 104. Alexiadou K, Anyiam O, Tan T. Cracking the combination: Gut hormones for the treatment of
 10 obesity and diabetes. *J Neuroendocrinol* 2019;**31**:e12664.
- 11 105. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B,
 12 Bunck MC, Stefanski A. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*
 13 2022;**387**:205-216.
- 14 106. Lau DCW, Erichsen L, Francisco AM, Satylganova A, le Roux CW, McGowan B, Pedersen SD,
 15 Pietiläinen KH, Rubino D, Batterham RL. Once-weekly cagrilintide for weight management in
 16 people with overweight and obesity: a multicentre, randomised, double-blind, placebo-
 17 controlled and active-controlled, dose-finding phase 2 trial. *Lancet* 2021;**398**:2160-2172.
- 18 107. Nahra R, Wang T, Gadde KM, Oscarsson J, Stumvoll M, Jermutus L, Hirshberg B, Ambery P.
 19 Effects of Cotadutide on Metabolic and Hepatic Parameters in Adults With Overweight or
 20 Obesity and Type 2 Diabetes: A 54-Week Randomized Phase 2b Study. *Diabetes Care*
 21 2021;**44**:1433-1442.
- 22 108. Meier JJ, Gallwitz B, Siepmann N, Holst JJ, Deacon CF, Schmidt WE, Nauck MA. Gastric inhibitory
 23 polypeptide (GIP) dose-dependently stimulates glucagon secretion in healthy human subjects at
 24 euglycaemia. *Diabetologia* 2003;**46**:798-801.
- 25 109. Khoo B, Tan TM. Combination gut hormones: prospects and questions for the future of obesity
 26 and diabetes therapy. *J Endocrinol* 2020;**246**:R65-r74.
- 27 110. Christensen MB, Gasbjerg LS, Heimbürger SM, Stensen S, Vilsbøll T, Knop FK. GIP's involvement
 28 in the pathophysiology of type 2 diabetes. *Peptides* 2020;**125**:170178.
- 29 111. Bergmann N, Lund A, Gasbjerg L, Meessen E, Andersen M, Bergmann S, Hartmann B, Holst J,
 30 Jessen L, Christensen M. Effects of combined GIP and GLP-1 infusion on energy intake, appetite
 31 and energy expenditure in overweight/obese individuals: a randomised, crossover study.
 32 *Diabetologia* 2019;**62**:665-675.
- 33 112. Bergmann NC, Gasbjerg LS, Heimbürger SM, Krogh LSL, Dela F, Hartmann B, Holst JJ, Jessen L,
 34 Christensen MB, Vilsbøll T, Lund A, Knop FK. No Acute Effects of Exogenous Glucose-Dependent
 35 Insulinotropic Polypeptide on Energy Intake, Appetite, or Energy Expenditure When Added to
 36 Treatment With a Long-Acting Glucagon-Like Peptide 1 Receptor Agonist in Men With Type 2
 37 Diabetes. *Diabetes Care* 2020;**43**:588-596.
- 38 113. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X,
 39 Brown K. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J*
 40 *Med* 2021;**385**:503-515.
- 41 114. Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, Urva S, Gimeno RE, Milicevic Z, Robins D,
 42 Haupt A. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in
 43 patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-
 44 controlled phase 2 trial. *Lancet* 2018;**392**:2180-2193.
- 45 115. Coskun T, Sloop K, Loghin C, Alsina-Fernandez J, Urva S, Bokvist K, Cui X, Briere D, Cabrera O,
 46 Roell W. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2
 47 diabetes mellitus: from discovery to clinical proof of concept. *Molecular Metabolism* 2018;**18**:3-
 48 14.

- 1 116. Willard FS, Douros JD, Gabe MB, Showalter AD, Wainscott DB, Suter TM, Capozzi ME, van der
2 Velden WJ, Stutsman C, Cardona GR, Urva S, Emerson PJ, Holst JJ, D'Alessio DA, Coghlan MP,
3 Rosenkilde MM, Campbell JE, Sloop KW. Tirzepatide is an imbalanced and biased dual GIP and
4 GLP-1 receptor agonist. *JCI Insight* 2020;**5**.
- 5 117. Ludvik B, Giorgino F, Jódar E, Frias JP, Fernández Landó L, Brown K, Bray R, Rodríguez Á. Once-
6 weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without
7 SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label,
8 parallel-group, phase 3 trial. *Lancet* 2021;**398**:583-598.
- 9 118. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, Aizenberg D, Wynne AG,
10 Riesmeyer JS, Heine RJ, Wiese RJ. Tirzepatide versus insulin glargine in type 2 diabetes and
11 increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group,
12 multicentre, phase 3 trial. *Lancet* 2021;**398**:1811-1824.
- 13 119. Dahl D, Onishi Y, Norwood P, Huh R, Bray R, Patel H, Rodríguez Á. Effect of Subcutaneous
14 Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With
15 Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. *Jama* 2022;**327**:534-545.
- 16 120. Sattar N, McGuire DK, Pavo I, Weerakkody GJ, Nishiyama H, Wiese RJ, Zoungas S. Tirzepatide
17 cardiovascular event risk assessment: a pre-specified meta-analysis. *Nat Med* 2022;**28**:591-598.
- 18 121. Iepsen EW, Lundgren J, Dirksen C, Jensen JE, Pedersen O, Hansen T, Madsbad S, Holst JJ, Torekov
19 SS. Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin
20 during maintenance of weight loss. *Int J Obes (Lond)* 2015;**39**:834-841.
- 21 122.
22 [https://sciencehub.novonordisk.com/content/dam/hcpexperience/kol/en/congresses/o](https://sciencehub.novonordisk.com/content/dam/hcpexperience/kol/en/congresses/ow/2021/ow21-step-5-primary-lb/pdfs/PPT_Garvey_Two_year_effect_semaglutide_2.4mg_STEP_5_no%20animations.pdf)
23 [w/2021/ow21-step-5-primary-](https://sciencehub.novonordisk.com/content/dam/hcpexperience/kol/en/congresses/ow/2021/ow21-step-5-primary-lb/pdfs/PPT_Garvey_Two_year_effect_semaglutide_2.4mg_STEP_5_no%20animations.pdf)
24 [lb/pdfs/PPT_Garvey_Two_year_effect_semaglutide_2.4mg_STEP_5_no%20animations.pdf](https://sciencehub.novonordisk.com/content/dam/hcpexperience/kol/en/congresses/ow/2021/ow21-step-5-primary-lb/pdfs/PPT_Garvey_Two_year_effect_semaglutide_2.4mg_STEP_5_no%20animations.pdf).
- 25 123. Ahlin S, Peltonen M, Sjöholm K, Anveden Å, Jacobson P, Andersson-Assarsson JC, Taube M,
26 Larsson I, Lohmander LS, Näslund I, Svensson PA, Carlsson LMS. Fracture risk after three
27 bariatric surgery procedures in Swedish obese subjects: up to 26 years follow-up of a controlled
28 intervention study. *J Intern Med* 2020;**287**:546-557.
- 29 124. Neovius M, Bruze G, Jacobson P, Sjöholm K, Johansson K, Granath F, Sundström J, Näslund I,
30 Marcus C, Ottosson J, Peltonen M, Carlsson LMS. Risk of suicide and non-fatal self-harm after
31 bariatric surgery: results from two matched cohort studies. *Lancet Diabetes Endocrinol*
32 2018;**6**:197-207.
- 33 125. Dehestani B, Stratford NR, le Roux CW. Amylin as a Future Obesity Treatment. *J Obes Metab*
34 *Syndr* 2021;**30**:320-325.
- 35 126. Enebo LB, Berthelsen KK, Kankam M, Lund MT, Rubino DM, Satynganova A, Lau DCW. Safety,
36 tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of
37 multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised,
38 controlled, phase 1b trial. *Lancet* 2021;**397**:1736-1748.
- 39 127. Habegger KM, Heppner KM, Geary N, Bartness TJ, DiMarchi R, Tschöp MH. The metabolic
40 actions of glucagon revisited. *Nat Rev Endocrinol* 2010;**6**:689-697.
- 41 128. Ambery P, Parker VE, Stumvoll M, Posch MG, Heise T, Plum-Moerschel L, Tsai LF, Robertson D,
42 Jain M, Petrone M, Rondinone C, Hirshberg B, Jeremias L. MEDI0382, a GLP-1 and glucagon
43 receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised,
44 controlled, double-blind, ascending dose and phase 2a study. *Lancet* 2018;**391**:2607-2618.
- 45 129. Tillner J, Posch MG, Wagner F, Teichert L, Hijazi Y, Einig C, Keil S, Haack T, Wagner M, Bossart M,
46 Larsen PJ. A novel dual glucagon-like peptide and glucagon receptor agonist SAR425899: Results
47 of randomized, placebo-controlled first-in-human and first-in-patient trials. *Diabetes Obes*
48 *Metab* 2019;**21**:120-128.

- 1 130. Bossart M, Wagner M, Elvert R, Evers A, Hübschle T, Kloeckener T, Lorenz K, Moessinger C,
2 Eriksson O, Velikyan I, Pierrou S, Johansson L, Dietert G, Dietz-Baum Y, Kissner T, Nowotny I,
3 Einig C, Jan C, Rharbaoui F, Gassenhuber J, Prochnow HP, Agueusop I, Porksen N, Smith WB,
4 Nitsche A, Konkar A. Effects on weight loss and glycemic control with SAR441255, a potent
5 unimolecular peptide GLP-1/GIP/GCG receptor triagonist. *Cell Metab* 2022;**34**:59-74.e10.
6 131. [https://diabetesjournals.org/diabetes/article/71/Supplement_1/340-OR/146500/340-OR-](https://diabetesjournals.org/diabetes/article/71/Supplement_1/340-OR/146500/340-OR-LY3437943-LY-a-Novel-Triple-GIP-GLP-1)
7 [LY3437943-LY-a-Novel-Triple-GIP-GLP-1](https://diabetesjournals.org/diabetes/article/71/Supplement_1/340-OR/146500/340-OR-LY3437943-LY-a-Novel-Triple-GIP-GLP-1).
8 132. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR.
9 Inhibition of food intake in obese subjects by peptide YY3-36. *N Engl J Med* 2003;**349**:941-948.
10 133. Tan TM, Minnion J, Khoo B, Ball LJ, Malviya R, Day E, Fiorentino F, Brindley C, Bush J, Bloom SR.
11 Safety and efficacy of an extended-release peptide YY analogue for obesity: A randomized,
12 placebo-controlled, phase 1 trial. *Diabetes Obes Metab* 2021;**23**:1471-1483.
13 134. Neary N, Small C, Druce M, Park A, Ellis S, Semjonous N, Dakin C, Filipsson K, Wang F, Kent A.
14 Peptide YY3-36 and glucagon-like peptide-17-36 inhibit food intake additively. *Endocrinology*
15 2005;**146**:5120-5127.
16 135. De Silva A, Salem V, Long C, Makwana A, Newbould R, Rabiner E, Ghatei M, Bloom S, Matthews
17 P, Beaver J. The gut hormones PYY 3-36 and GLP-1 7-36 amide reduce food intake and
18 modulate brain activity in appetite centers in humans. *Cell Metabolism* 2011;**14**:700-706.
19 136. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, De Waele K, Farooqi IS,
20 Gonneau-Lejeune J, Gordon G, Kohlsdorf K, Poitou C, Puder L, Swain J, Stewart M, Yuan G,
21 Wabitsch M, Kühnen P. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals
22 with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase
23 3 trials. *Lancet Diabetes Endocrinol* 2020;**8**:960-970.
24 137. Heymsfield SB, Coleman LA, Miller R, Rooks DS, Laurent D, Petricoul O, Praestgaard J, Swan T,
25 Wade T, Perry RG, Goodpaster BH, Roubenoff R. Effect of Bimagrumb vs Placebo on Body Fat
26 Mass Among Adults With Type 2 Diabetes and Obesity: A Phase 2 Randomized Clinical Trial.
27 *JAMA Netw Open* 2021;**4**:e2033457.
28 138. Fournier B, Murray B, Gutzwiller S, Marcaletti S, Marcellin D, Bergling S, Brachat S, Persohn E,
29 Pierrel E, Bombard F, Hatakeyama S, Trendelenburg AU, Morvan F, Richardson B, Glass DJ, Lach-
30 Trifilieff E, Feige JN. Blockade of the activin receptor IIb activates functional brown adipogenesis
31 and thermogenesis by inducing mitochondrial oxidative metabolism. *Mol Cell Biol* 2012;**32**:2871-
32 2879.
33 139. Capristo E, Panunzi S, De Gaetano A, Spuntarelli V, Bellantone R, Giustacchini P, Birkenfeld AL,
34 Amiel S, Bornstein SR, Raffaelli M, Mingrone G. Incidence of Hypoglycemia After Gastric Bypass
35 vs Sleeve Gastrectomy: A Randomized Trial. *J Clin Endocrinol Metab* 2018;**103**:2136-2146.
36 140. Inagaki N, Takeuchi M, Oura T, Imaoka T, Seino Y. Efficacy and safety of tirzepatide monotherapy
37 compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a
38 double-blind, multicentre, randomised, phase 3 trial. *Lancet Diabetes Endocrinol* 2022.
39 141. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B,
40 Nissen SE, Bhatt DL. Bariatric surgery versus intensive medical therapy in obese patients with
41 diabetes. *N Engl J Med* 2012;**366**:1567-1576.
42 142. Kadowaki T, Chin R, Ozeki A, Imaoka T, Ogawa Y. Safety and efficacy of tirzepatide as an add-on
43 to single oral antihyperglycaemic medication in patients with type 2 diabetes in Japan (SURPASS
44 J-combo): a multicentre, randomised, open-label, parallel-group, phase 3 trial. *Lancet Diabetes*
45 *Endocrinol* 2022.

1 **Figure 1.** The effect of different weight loss interventions [low calorie diet, exercise,
2 pharmacotherapy (GLP-1 receptor analogues) and bariatric surgery] on appetite.

3 **Figure 2.** The efficacy gap in weight loss between lifestyle interventions, approved
4 pharmacotherapies for obesity over last decade (plus tirzepatide) and bariatric surgery in adults
5 without type 2 diabetes (Figure 2A) and in adults with type 2 diabetes (Figure 2B).

6 Data in Figure 2A is based on published clinical trials used a) lifestyle interventions (500 kcal
7 deficit diet plus advise for physical activity or intensive behavioural therapy) plus placebo (green
8 background),^{15, 62, 69-71, 84, 85} b) liraglutide 3mg,^{84, 85} naltrexone/bupropion 32/360,⁶⁹⁻⁷¹
9 phentermine/topiramate 15/92,⁶² semaglutide 2.4mg^{15, 95, 100, 101} and tirzepatide 5mg and 15mg¹⁰⁵
10 plus lifestyle interventions (approved obesity pharmacotherapies plus tirzepatide, orange
11 background) or c) sleeve gastrectomy¹³⁹ and Roux-en-Y gastric bypass¹³⁹ (bariatric surgery, blue
12 background) in adults without type 2 diabetes. Data in Figure 2B is based on published clinical
13 trials used a) lifestyle interventions (500 kcal deficit diet plus advise for physical activity or
14 intensive behavioural therapy) plus placebo (green background),^{64, 72, 87, 97} b) liraglutide 3mg,^{86, 87}
15 naltrexone/bupropion 32/360,⁷² phentermine/topiramate 15/92,⁶⁴ semaglutide 2.4mg⁹⁷ plus
16 lifestyle interventions and tirzepatide 5mg and 15mg^{117, 118, 140} (approved obesity
17 pharmacotherapies plus tirzepatide, orange background) or c) sleeve gastrectomy¹⁴¹ and Roux-
18 en-Y gastric bypass¹⁴¹ (bariatric surgery, blue background) in adults with type 2 diabetes.

19 **Figure 3.** Categorical weight loss ($\geq 10\%$ in Figure 3A, $\geq 15\%$ in Figure 3B) in large clinical
20 trials with the approved obesity pharmacotherapies over the last decade (plus tirzepatide) in
21 people with and without type 2 diabetes (studies with follow-up 52-72 weeks).

- 1 **Table 1.** Large multi-centre clinical trials for approved obesity pharmacotherapies over last decade and tirzepatide in populations without diabetes (or with
2 majority of participants without diabetes)

	Lifestyle intervention	Comparator	Duration (week)	BMI baseline (drug/comparator)	WL % (drug/comparator) ETD	≥5% WL (%) (drug/comparator)	≥10% WL (%) (drug/comparator)	≥15% WL (%) (drug/comparator)	Comment
Phentermine/ Topiramate ER 3.75/23, 7.5/46 or 15/92									
Gadde, 2011 ⁶⁵ CONQUER (7.5/46 and 15/92)	500 kcal/day deficit diet + advise for PA	vs placebo	56	36.6/ 36.7	-7.8% to -9.8%/ -1.2% ETD: -6.6% to -8.6%	62 to 70/ 21	37 to 48/ 7	NR	15.6% of participants had T2D
Allison, 2012 ⁶² EQUIP (3.75/23 and 15/92)	500kcal/d deficit diet + advise for PA	vs placebo	56	41.9 to 42.6/ 42.0	-5.1% to -10.9%/ -1.56% ETD: -3.54% to -9.34%	44.9 to 66.7/ 17.3	18.8 to 47.2/ 7.4	7.3 to 32.3/ 3.4	
Garvey 2012 ⁶³ SEQUEL (7.5/46 and 15/92)	500kcal/d deficit diet + advise for PA	vs placebo	108	36.1 to 36.2/ 36	-9.3% to -10.5%/ -1.8% ETD: -7.5% to -9.7%	75.2 to 79.3/ 30	50.3 to 53.9/ 11.5	24.2 to 31.9/ 6.6	
Naltrexone/ Bupropion SR 16/360 or 32/360									
Greenway 2010 ⁶⁹ COR-I (16/360 and 32/360)	500kcal/d deficit diet + advise for PA	vs placebo	56	36.1 to 36.2/ 36.2	-5.0% to -6.1%/ -1.3% ETD: -3.7% to -4.8%	39 to 48/ 16	20 to 25/ 7	9 to 12/ 2	
Apovian 2013 ⁷⁰ COR-II (32/360)	500kcal/d deficit diet + advise for PA	vs placebo	56	36.2/ 36.1	-6.4% / -1.2% ETD: -5.2%	50.5/ 17.1	28.3/ 5.7	13.5/ 2.4	Primary outcome was at 28 weeks
Wadden 2011 ⁷¹ COR-BMOD (32/360)	IBT – 28 group sessions plus calorie deficit diet and advise for PA	vs placebo	56	36.3/ 37	-9.3%/ -5.1% ETD: -4.2%	66.4/ 42.5	41.5/ 20.2	29.1/ 10.9	
Liraglutide 3mg									
Pi-Sunyer 2015 ⁸⁴ SCALE-Obesity	500 kcal deficit diet + advise for PA	vs placebo	56	38.3/ 38.3	-8.0%/ -2.6% ETD: -5.4%	63.2/ 27.1	33.1/ 10.6	14.4/ 3.5	
Le Roux 2017 ⁸⁸ SCALE-Prediabetes	500 kcal deficit diet + advise for PA	vs placebo	160	38.8/ 39.0	-6.1%/ -1.9% ETD: -4.3%	49.6/ 23.7	24.8/ 9.9	11/ 3.1	79% reduction at the risk of developing diabetes in people with prediabetes
Wadden 2020 ⁸⁵ SCALE-IBT	IBT – 23 brief sessions plus diet 1200-1800kcal/d + advise for PA	vs placebo	56	39.3/ 38.7	-7.5%/ -4.0% ETD: -3.4%	61.5/ 38.8	30.5/ 19.8	18.1/ 8.9	

Wadden 2013 ⁴¹ SCALE -Maintenance	500kcal deficit diet after achieving >5% WL with 1200-1400kcal diet	vs placebo	56	36/ 35.2	-6.2%/ -0.2% ETD: -6.1%	50.5/ 21.8	26.1/ 6.3	NR	Weight maintenance study – participants randomised after they have achieved >5% weight loss with diet
Blackman 2016 ⁹⁰ SCALE sleep apnea	500 kcal deficit diet + advise for PA	vs placebo	32	38.9/ 39.4	-5.7%/ -1.6% ETD: -4.2%	46.3/ 18.5	23.4/ 1.7	NR	Apnoea Hypopnea Index (events/hour) reduced by 6.1 events/hour
Kelly 2020 ⁸³ Liraglutide for Adolescents with Obesity	Individualised counselling on healthy nutrition + advise for PA for 60min/d	vs placebo	56	35.3/ 35.8	-2.65%/ +2.37% ETD: -5.01%	43.3/ 18.7	26.1/ 8.1	NR	Participants were adolescents 12 to <18 years old
Semaglutide 2.4mg*									
Wilding, 2021 ¹⁵ STEP-1	500 kcal/day deficit diet + advise for PA	vs placebo	68	37.8/ 38.0	-14.9%/ -2.4% ETD: -12.4%	86.4/ 31.5	69.1/ 12	50.5/ 4.9	
Wadden 2013 ⁹⁶ STEP-3	Low calorie diet (1000-1200kcal) for 8 weeks and IBT (30 counselling sessions)	vs placebo	68	38.1/ 37.8	-16%/ -5.7% ETD: -10.3%	86.6/ 47.6	75.3/ 27	55.8/ 13.2	
Rubino, 2021 ¹⁰⁰ STEP-4	500 kcal/day deficit diet + advise for PA	vs placebo	0 → 68 20 → 68	38.4 34.5/ 34.1	-17.4%/ -5.0% -7.9% / +6.9% ETD: -14.8%	88.7/ 47.6	79/ 20.4	63.7/ 9.2	Medication withdrawal study – all participants received Semaglutide 2.4mg for 20 weeks and then randomised to placebo vs Semaglutide 2.4mg for next 48 weeks
Kadowaki 2022 ¹⁰¹ STEP-6	500 kcal/day deficit diet + advise for PA	vs placebo	68	86.9/ 90.2	-13.2%/ -2.1% ETD: -11.06%	83/ 21	61/ 5	41/ 3	Study in East Asian population (Japan, South Korea) -25% of participants had T2D
Rubino, 2022 ⁹⁵ STEP-8	500 kcal/day deficit diet + advise for PA	vs liraglutide 3mg	68	37/ 37.2	-15.8%/ -6.4% ETD: -9.4%	87.2/ 58.1	70.9/ 25.6	55.6/ 12.0	
Tirzepatide 5-15mg*									
Jastreboff A, 2022 ¹⁰⁵ SURMOUNT-1	500 kcal/day deficit diet and advise for PA	vs placebo	72	37.4 to 38.2/ 38.2	-15.0% to -20.9%/ -3.1% ETD: -11.9% to -17.8%	85.1 to 90.9/ 34.5	68.5 to 83.5/ 18.8	48.0 to 70.6/ 8.8	

1 WL: Weight loss, ER: Extended release, SR: Slow release, ETD: Estimated treatment difference, PA: physical activity, IBT: Intensive Behavioural Therapy, T2D: Type 2 Diabetes, *data presented as
2 treatment-policy estimand

3

4

5

6

1 **Table 2.** Large multi-centre clinical trials for approved obesity pharmacotherapies over last decade and tirzepatide in people with type 2 diabetes.

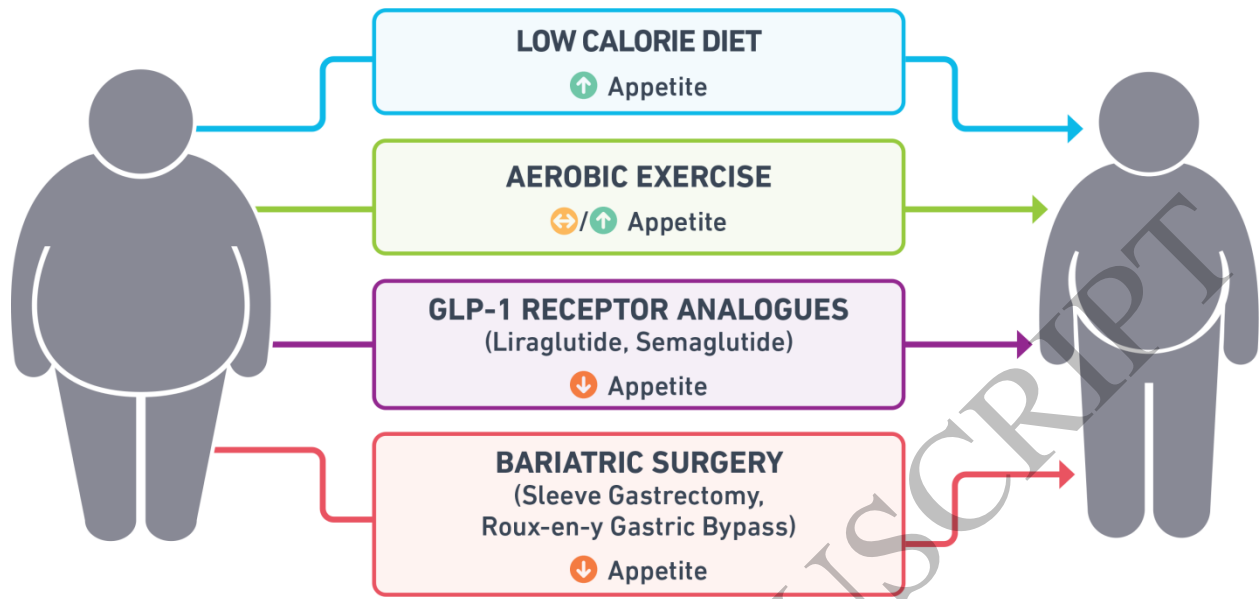
	Lifestyle change	Comparator	Background therapy	Duration (week)	BMI baseline (drug/comparator)	Weight loss (drug/comparator) ETD vs comparator	HbA1C (%) baseline (drug/comparator)	HbA1C (%) change (drug/comparator) ETD: -0.4%	≥10% WL (%) (drug/comparator)	≥15% WL (%) (drug/comparator)	HbA1C ≤7% (drug/comparator)
Phentermine/ Topiramate ER 15/92											
Garvey 2014 ⁶⁴ OB-202/DM-230	500kcal/day deficit diet and advise for PA	vs placebo	Diet ± oral glucose lowering meds	56	35.5/ 35.2	-9.6%/ -2.6% ETD: -7%	8.8/8.5	-1.6%/ -1.2% ETD: -0.4%	37/9	NR	53/40
Naltrexone/ Bupropion SR 32/360											
Hollander 2013 ⁷² COR-Diabetes	500 kcal/d deficit diet + advise for PA	vs placebo	Not on or stable dose glucose-lowering meds	56	36.7/ 36.3	-5.0%/ -1.8% ETD: -3.2%	8.0/ 8.0	-0.6%/ -0.1% ETD: -0.5%	26.3/ 8.0		44.1/ 26.3
Liraglutide 3mg											
Davies 2015 ⁸⁷ SCALE Diabetes	500 kcal/d deficit diet + advise for PA	vs placebo	diet +exercise or ≤ 3 oral glucose – lowering meds	56	37.1/ 37.4	-6.0% / -2.0% ETD: -4%	7.9/ 7.9	-1.3/ -0.3 ETD: -0.93	25.2/ 6.7	NR	69.2/ 27.2
		vs liraglutide 1.8mg			37.1/ 37.4	-6.0%/ -4.7% ETD: -1.3%	7.9/ 8.0	-1.3 / -1.1 ETD: -0.2	25.2/ 15.9		69.2/ 66.7
Garvey 2020 ⁸⁶ SCALE-Insulin	IBT – 23 sessions	vs placebo	Basal insulin + ≤ 2 oral glucose-lowering meds	56	35.9/ 35.3	-5.8%/ -1.5% ETD: -4.3%	7.9/ 8.0	-1.1/ -0.6 ETD: -0.5	22.8/ 6.6	NR	NR
Semaglutide 2.4mg*											
Davies 2021 ⁹⁷ STEP-2	500 kcal/d deficit diet + advise for PA	vs placebo	diet +exercise or ≤ 3 oral glucose – lowering meds	68	35.9/ 35.9	-9.64%/ -3.42% ETD: -6.21%	8.1/ 8.1	-1.6/ -0.4 ETD: -1.2	45.6/ 8.2	25.8/3.2	78.5/ 26.5
		vs semaglutide 1mg			35.9/ 35.3	-9.64%/ -6.99% ETD: -2.65%	8.1/ 8.1	-1.6/ -1.5 ETD: -0.2	45.6/ 28.7	25.8/13.7	78.5/ 72.3

Tirzepatide 5-15mg											
Rosenstock 2021 ¹⁴ SURPASS-1*	No new diet or exercise programme	vs placebo	Diet and exercise	40	31.5 to 32.2/ 31.7	-6.3 to -7.8kg/ -1.0kg ETD: -5.3kg to -6.8kg	7.85 to 7.97/ 8.05	-1.69 to -1.75/ -0.09 ETD: -1.6 to -1.66	27 to 38/ 0	12 to 23/ 0	78 to 85/ 23
Frias 2021 ¹¹³ SURPASS-2*	Not described	vs semaglutide 1mg	Metformin ≥ 1500mg/d	40	33.8 to 34.5/ 34.2	-7.6 to -11.2kg/ -5.7kg ETD: -1.9 to -5.5kg	8.26 to 8.32/ 8.25	-2.01 to -2.3/ -1.86 ETD: -0.15 to -0.45	34 to 57/ 24	15 to 36/ 8	82 to 86/ 79
Ludvik 2021 ¹¹⁷ SURPASS-3*	Not described	vs insulin degludec	Metformin ± SGLT-2i	52	33.4 to 33.7/ 33.4	-7 to -11.3kg/ +1.9kg ETD: -8.9 to -13.2kg	8.17 to 8.21/ 8.12	-1.85 to -2.14/ -1.25 ETD: -0.60 to -0.89	35 to 58/ 3	12 to 35/ 0	79 to 83/ 58
Del Prato 2021 ¹¹⁸ SURPASS-4*	Not described	vs insulin glargine	≤ 3 oral glucose-lowering meds	52	32.5 to 32.8/ 32.5	-6.4 to -10.6kg/ +1.7kg ETD: -8.1 to -12.3kg	8.52 to 8.60/ 8.51	-2.11 to -2.41/ -1.39 ETD: -0.72 to -1.02	32 to 59/ 2	13 to 33/ <1	75 to 85/ 49
Dahl 2021 ¹¹⁹ SURPASS-5*	Not described	vs placebo	Insulin glargine ± metformin	40	33.4 to 33.6/ 33.2	-5.4 to -8.8kg/ +1.6kg ETD: -7.1 to -10.5kg	8.23 to 8.36/ 8.37	-2.11 to -2.40/ -0.86 ETD: -1.24 to -1.53	21 to 42/ 1	7 to 24/ 0	85 to 90/ 35
Inagaki N ¹⁴⁰ SURPASS J-mono (Japanese population)	Not described	vs dulaglutide 0.75mg	Diet and exercise	52	28 to 28.6/ 27.8	-5.4 to -9.4kg/ -0.4kg* ETD: -4.9 to -8.9kg	8.2 / 8.2	-2.24 to -2.57/ -1.27* ETD: -1.1 to -1.5	34 to 67/ 3**	16 to 45/ <1**	94 to 99/ 67**
Kadowaki T ¹⁴² SURPASS J-combo** (Japanese population)	Not described	no comparator	1 oral glucose-lowering med	52	27.6 to 28.4	-3.8 to -10.3kg**	8.5 to 8.6	-2.5 to -3**	20 to 64**	7 to 41**	93 to 98**

1 WL: Weight loss, ER: Extended release, SR: Slow release, ETD: Estimated treatment difference, PA: physical activity, IBT: Intensive Behavioural Therapy, T2D: Type 2 Diabetes, SGLT-2i: Sodium-glucose co-transporters inhibitor, *data presented as treatment-policy estimand, **data presented as efficacy estimand, as there is no available data for treatment-policy estimand.

3

4



1

2

Figure 1

ACCEPTED MANUSCRIPT

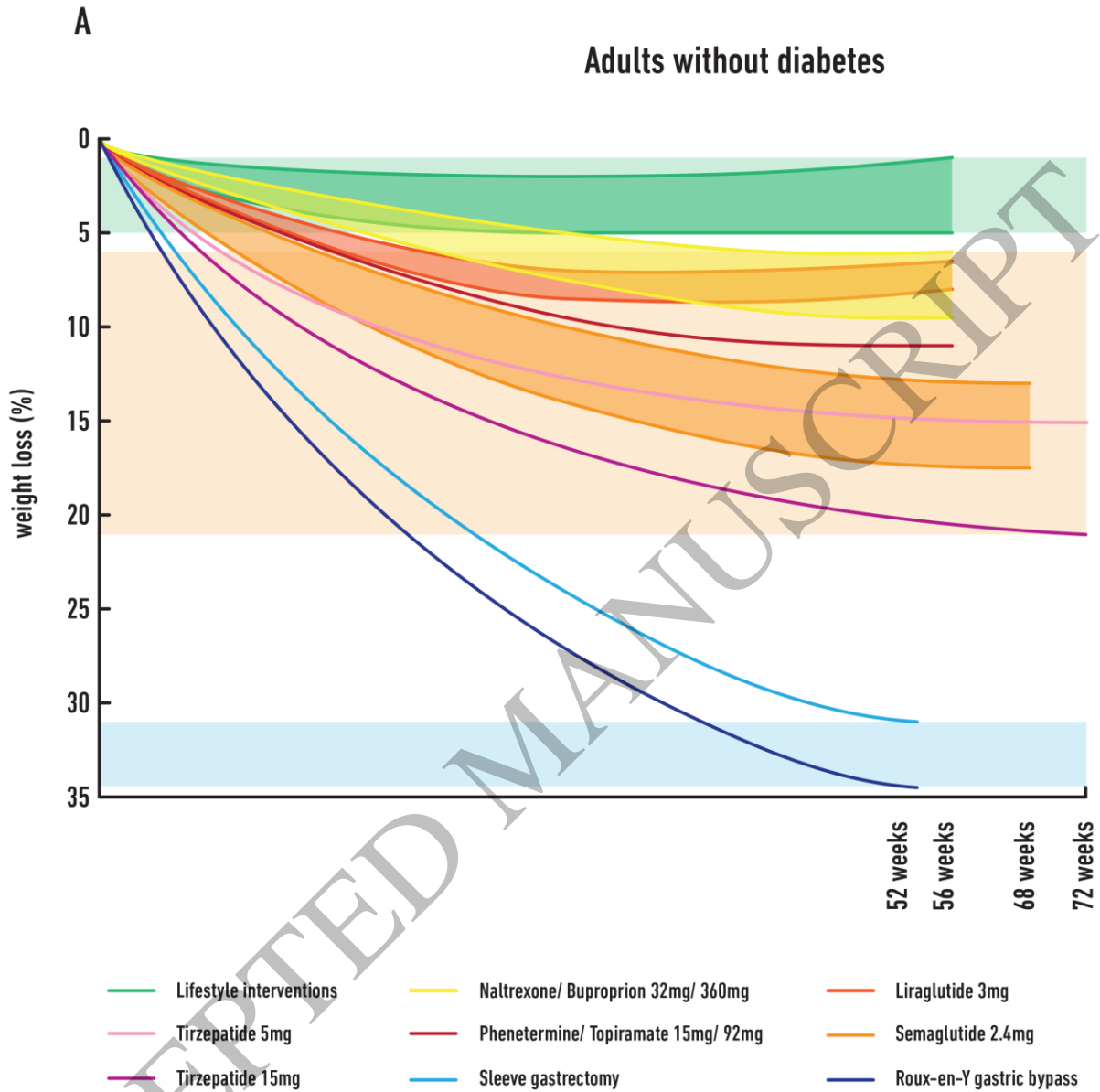


Figure 2
160x159 mm (.47 x DPI)

1
2
3
4

A



Figure 3A
246x105 mm (.47 x DPI)

1
2
3
4

ACCEPTED MANUSCRIPT

Downloaded from <https://academic.oup.com/ cardiovascular/advance-article/doi/10.1093/cvr/cvac176/6854907> by guest on 16 December 2022

A

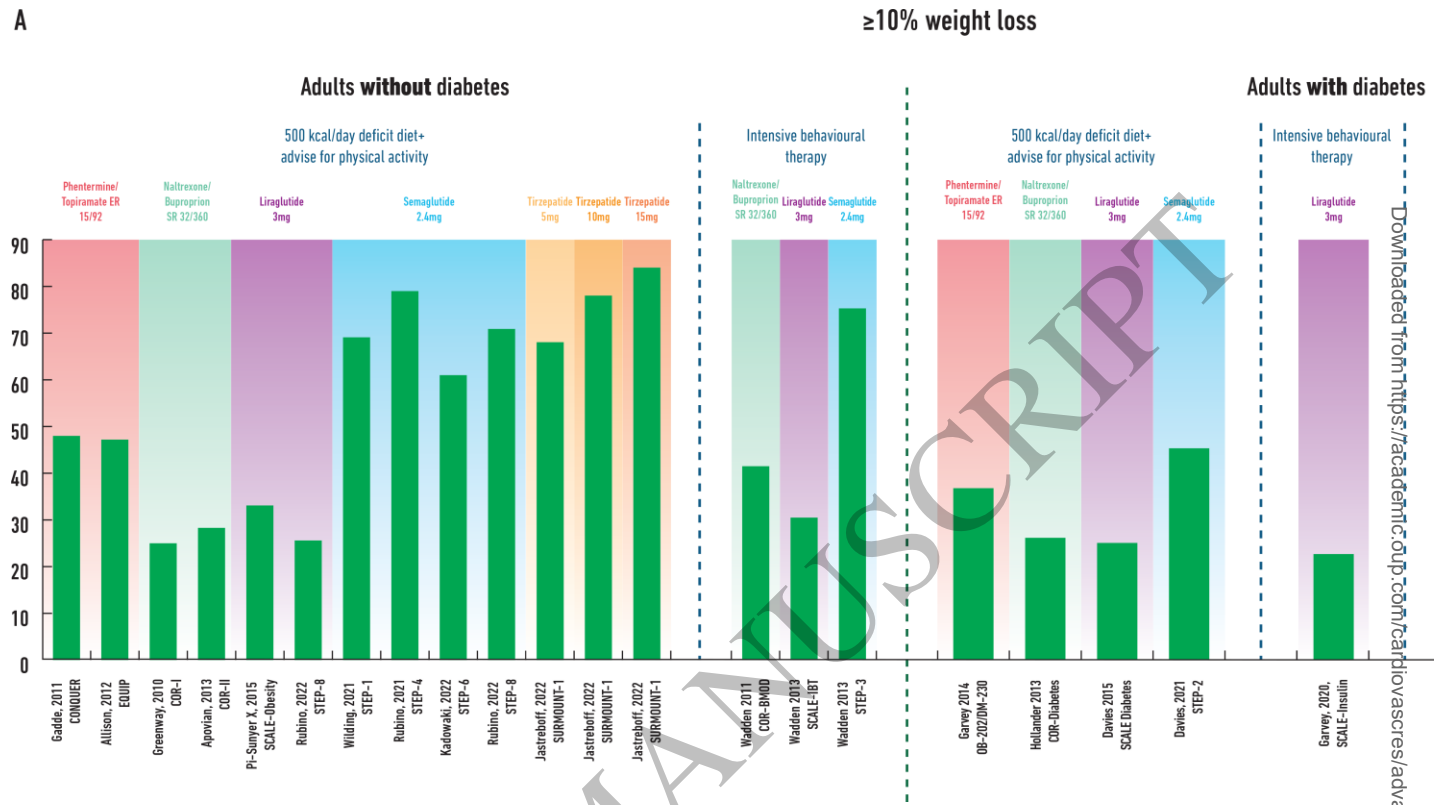


Figure 3B
246x105 mm (.47 x DPI)

1
2
3
4

ACCEPTED MANUSCRIPT

Downloaded from <https://academic.oup.com/cvri/advance-article/doi/10.1093/cvri/cvac176/6854907> by guest on 16 December 2022